In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: January 8, 2025

ROBERT JURANEK,	*	PUBLISHED
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Petitioner,	*	No. 19-226V
	*	
v.	*	Special Master Nora Beth Dorsey
	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Dismissal; Influenza ("Flu") Vaccine; Multiple Sclerosis ("MS"); Significant Aggravation.
	*	
Respondent.	*	
	*	

Edward Kraus, Kraus Law Group, LLC, Chicago, IL, for Petitioner.
Benjamin Patrick Warder, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION[1]

On February 8, 2019, Robert Juranek ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10 et seq. (2018).[2] Petitioner alleged that an influenza ("flu") vaccination administered on October 7, 2016 significantly aggravated his stable and asymptomatic multiple sclerosis ("MS"). Petition at Preamble (ECF No. 1); Petitioner's Pre-Hearing Memorandum

[1] Because this Decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2018) ("Vaccine Act" or "the Act"). All citations in this Decision to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

("Pet. Memo."), filed Feb. 6, 2024, at 8 n.1 (ECF No. 99).[3] Respondent argued against compensation, stating that "this case is not appropriate for compensation under the terms of the [Vaccine] Act." Respondent's Report ("Resp. Rept.") at 1 (ECF No. 27).

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards,[4] the undersigned finds that Petitioner has failed to provide preponderant evidence that his flu vaccination significantly aggravated his MS. Thus, Petitioner has failed to satisfy his burden of proof under Loving v. Secretary of Health & Human Services, 86 Fed. Cl. 135, 142-44 (2009). Accordingly, the petition must be dismissed.

I. ISSUES TO BE DECIDED

The parties dispute whether Petitioner "experienced a significant worsening of his MS[5] following the [flu] vaccination on October 7, 2016." Joint Prehearing Submission, filed Feb. 27, 2024, at 1 (ECF No. 107). And if so, the parties dispute the time frame for the onset of Petitioner's symptoms. Id.

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[3] In his petition, Petitioner alleged he developed peripheral neuropathy and MS, or alternatively, developed peripheral neuropathy and experienced a significant aggravation of previously stable and asymptomatic MS, which were caused-in-fact by a flu vaccination administered on October 7, 2016. Petition at Preamble. In his prehearing submission, Petitioner explained he abandoned his causation-in-fact claim and "[was] proceeding solely on a claim for significant aggravation." Pet. Memo. at 8 n.1. Accordingly, the undersigned limits the scope of this decision to significant aggravation of MS and does not discuss a causation-in-fact claim or a diagnosis other than MS.

[4] While the undersigned has reviewed all of the information filed in this case, only those filings and records that are most relevant will be discussed. See Moriarty v. Sec'y of Health & Hum. Servs., 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision."); see also Paterek v. Sec'y of Health & Hum. Servs., 527 F. App'x 875, 884 (Fed. Cir. 2013) ("Finding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered.").

[5] MS is a chronic disease of the central nervous system ("CNS") that results in increased impairment and disability over time. Resp. Ex. F, Tab 3 at 1 (Fred Lublin et al., Effect of Relapses on Development of Residual Deficit in Multiple Sclerosis, 61 Neurology 1528 (2003)). It is characterized by "monophasic clinical episode[s] with patient-reported symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 h[ours], with or without recovery, and in the absence of fever or infection." Resp. Ex. C, Tab 1 at 2 (Alan J. Thompson et al., Diagnosis of Multiple Sclerosis: 2017 Revisions of the McDonald Criteria, 17 Lancet Neurology 162 (2018)) (also cited as Resp. Ex. F, Tab 1). Diagnosis is made when both dissemination in time ("development or appearance of new CNS lesions over time") and dissemination in space ("development of lesions in distinct anatomical locations within the CNS") are met, and other diagnoses are ruled out. Id. at 2, 7. Objective evidence of lesions on MRI and oligoclonal bands in the CSF aid in the diagnosis of MS. Id. at 5.

Additionally, the parties dispute "[w]hether the [flu] vaccine administered to [Petitioner] on October 7, 2016 resulted in a significant aggravation of his MS pursuant to the Loving analysis." Joint Prehearing Submission at 2.

II. BACKGROUND

A. Procedural History

On February 8, 2019, Petitioner filed a petition, followed by medical records from March 2019 to October 2019.[6] Petition; Pet. Exhibits ("Exs.") 1-23. Respondent filed his Rule 4(c) report on January 30, 2020, arguing against compensation. Resp. Rept. at 1.

From March 29, 2021 to August 29, 2022, Petitioner filed expert reports from Dr. Lawrence Steinman and Respondent filed expert reports from Dr. Robert Fujinami and Dr. Amanda Piquet. Pet. Exs. 28-29, 56; Resp. Exs. A, C, E-G.

An entitlement hearing was held on April 2 and April 3, 2024. Order dated Apr. 3, 2024 (ECF No. 121). The transcript of the hearing was filed on May 6, 2024, and on June 3, 2024, the parties filed a joint status report indicating they did not wish to file post-hearing briefs. Joint Status Rept., filed June 3, 2024 (ECF No. 127).

This matter is now ripe for adjudication.

B. Factual History

1. Stipulated Facts

The parties agreed to the following stipulated facts in their Joint Prehearing Submission. See Joint Prehearing Submission at 1.

Petitioner was born on May 30, 1954. Joint Prehearing Submission at 1. Petitioner received a flu vaccine on October 7, 2016. Id. Prior to this vaccination, Petitioner "was not experiencing any symptoms related to [MS]." Id.

2. Summary of Medical Records[7]

Petitioner, who worked as a physician, was 62 years old when he received a flu vaccination on October 7, 2016. Pet. Ex. 1 at 33; Pet. Ex. 14 at 1. Prior to vaccination,

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[6] Petitioner continued to file medical records and affidavits throughout litigation.

[7] This summary of medical records is largely taken from the parties' prehearing briefs, as the undersigned finds they provided an accurate representation of the records. See Pet. Memo. at 1-7; Resp. Prehearing Brief, filed Mar. 5, 2024, at 3-14 (ECF No. 108). The summary has been edited by the undersigned.

Petitioner had a medical history including hemoglobinopathy,[8] right-sided cubital tunnel syndrome,[9] and a neurological event that occurred approximately 30 years earlier. Pet. Ex. 1 at 33-34.

On November 2, 2016, Petitioner saw a urologist, reporting a one-year history of urinary tract symptoms. Pet. Ex. 17 at 15-17. Review of systems documented no neurological symptoms, including muscle weakness or numbness, reported by Petitioner. Id. at 16. Neurologic examination revealed a normal gait. Id. Petitioner returned for a follow-up visit on January 25, 2017, and again, no muscle weakness or numbness were reported, and neurologic examination again showed a normal gait. Id. at 11-13.

On May 23, 2017, Petitioner underwent multiple laboratory tests, including tests for erythrocyte sedimentation rate, C-reactive protein, vitamin B-12, folate, and thyroid-stimulating hormone, and all were normal. Pet. Ex. 16 at 1-7.

On June 14, 2017, more than eight months after his flu vaccination, Petitioner saw neurologist Todd Elmore, M.D., for complaints of neuropathy. Pet. Ex. 1 at 33-36. Petitioner reported "a few weeks" after his receipt of a flu vaccine, "he started getting numbness in both of his feet." Id. at 1. Petitioner described this numbness as "tingling paresthesia" that was bilateral and symmetric. Id. The numbness ascended to about his mid-calf. Id. Petitioner further reported loss of sensation, but "no definite weakness," and no abnormalities in his hands. Id. It was noted that Petitioner had a history of encephalitis about 30 years earlier, for which "[h]e recovered pretty well from," and that he had a brother with a history of Guillain-Barré syndrome ("GBS").[10] Id. On examination, Petitioner exhibited normal muscle strength, muscle tone, gait, and balance. Id. at 35. Sensory examination was abnormal, revealing "decreased sensation to light touch in a distal pattern in his feet." Id. at 36. Petitioner also had "slightly decrease[d] reflexes throughout and nearly absent reflexes at [his] ankles." Id. Dr. Elmore's assessment was

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[8] Hemoglobinopathy refers to "any inherited disorder caused by abnormalities of hemoglobin, including sickle cell anemia, hemolytic anemia, or thalassemia," and "sometimes more specifically, a hemoglobin disorder involving a variation or variations of a globin chain, such as changes or substitutions in the amino acid sequences or moving of a chain from its usual place in the molecule." Hemoglobinopathy, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=22040 (last visited Dec. 6, 2024).

[9] Cubital tunnel syndrome is "a type of entrapment neuropathy with a complex of symptoms resulting from injury or compression of the ulnar nerve at the elbow, including pain and numbness along the ulnar aspect of the hand and forearm and weakness of the hand." Cubital Tunnel Syndrome, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=110481 (last visited Dec. 6, 2024).

[10] GBS is a "rapidly progressive ascending motor neuron paralysis of unknown etiology" that "begins with paresthesias of the feet, followed by flaccid paralysis of the entire lower limbs, ascending to the trunk, upper limbs, and face." Guillain-Barré Syndrome, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=110689 (last visited Dec. 6, 2024).

"[s]ensory neuropathy. It started fairly abruptly after a flu shot. Some concerns about [chronic inflammatory demyelinating polyneuropathy ("CIDP")]." Id. Testing was ordered. Id.

Petitioner underwent an electromyography ("EMG")/nerve conduction study ("NCS") on June 21, 2017, which revealed axonal neuropathy of the peroneal nerves[11] bilaterally, axonal and demyelinating sensory neuropathy of the bilateral lower extremities, and normal bilateral median motor nerves. Pet. Ex. 1 at 27-29. On June 28, 2017, lumbar puncture revealed normal levels of glucose and protein in his cerebrospinal fluid ("CSF") and more than five well-defined oligoclonal bands in the CSF that were not present in the serum, which was "supportive evidence of [MS]."[12] Id. at 16-23.

On August 30, 2017, Petitioner had a thoracic spine magnetic resonance imaging ("MRI") without contrast, which showed "[s]ubtle intramedullary signal abnormalities within the T1-T2 and T10-T11 cord segments without significant cord expansion. Differential considerations include demyelinating or infectious/inflammatory etiologies." Pet. Ex. 1 at 14-15. Ischemic or neoplastic causes were determined unlikely given the multifocality of the lesions and the lack of significant cord expansion. Id. at 15. A lumbar spine MRI without contrast, performed on the same day, showed multilevel degenerative changes. Id. at 5-6.

Petitioner returned to Dr. Elmore for a follow-up appointment on September 6, 2017. Pet. Ex. 1 at 1-4. Petitioner reported worsening numbness and tingling in his feet that "[h]e felt [] was ascending" and remained bilateral and symmetric. Id. at 1. Dr. Elmore documented Petitioner also reported "something that sounds like banding over his left flank" that Petitioner thought "started a few weeks prior to [] his [August 30, 2017] MRI," but "it [was] hard to say for sure" when it began. Id. On examination, Petitioner's reflexes and sensation were now normal, as was his coordination, strength, muscle tone, and gait. Id. at 3-4. Dr. Elmore noted that Petitioner's "bilateral[,] symmetric, ascending numbness and tingling [] started about [four] to [six] weeks after having a flu shot in October of last year." Id. at 4. He also stated that Petitioner had a "mildly abnormal NC[S] of his legs with mainly sensory findings and some slightly decreased amplitude and velocities consistent with a possible CIDP." Id. Petitioner had normal protein in his CSF, but oligoclonal bands in his CSF and demyelinating lesions in his thoracic spine, which Dr. Elmore opined was concerning for MS. Id. Dr. Elmore wrote "[i]t is certainly possible that his flu shot triggered an acute disseminated encephalomyelitis (ADEM) picture." Id. And he noted, "[t]his was caused by his flu shot (there is a very strong temporal correlation here)." Id. Dr. Elmore ordered MRIs of Petitioner's brain and cervical spine, with and without contrast, and he started Petitioner on gabapentin. Id.

An MRI of Petitioner's brain, performed September 13, 2017, revealed "[m]ultiple . . . T2/FLAIR abnormalities with involvement of the corpus callosum," which were "suggestive of

[11] Peroneal nerve is an "accessory deep fibular nerve." Nervus Fibularis Profundus Accessorius, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=92364 (last visited Dec. 6, 2024).

[12] "Oligoclonal bands are present in the CSF of more than 85% of patients with clinically definite [MS]." Pet. Ex. 1 at 23.

underlying demyelinating process, specifically [MS]. Some of the white matter abnormalities could potentially be related to small vessel disease as well." Pet. Ex. 1 at 8-9. No enhancing lesions were present to suggest active demyelination. Id. An MRI of Petitioner's cervical spine, also performed on September 13, 2017, revealed "[p]atchy cord signal abnormalities . . . suggestive of an underlying demyelinating process, specifically [MS]," but again there were no enhancing lesions to suggest active demyelination. Id. at 11-13.

Petitioner returned to see Dr. Elmore on October 4, 2017. Pet. Ex. 4 at 26-29. He complained of "worsening numbness," weakness in his arms, and "some numbness in his feet" described as "tingling paresthesia" that had worsened. Id. at 26. Petitioner also had cognitive complaints, including forgetfulness and difficulty concentrating, as well as fatigue and difficulty ambulating later in the day. Id. Examination revealed "slightly decreased sensation distally," "slightly diminished" deep tendon reflexes distally, diffuse weakness, and "a little unstead[iness] on his feet." Id. at 28-29. Assessment was "clinically definite MS." Id. at 29. Dr. Elmore noted Petitioner "ha[d] a very classic looking MRI (which looks pretty bad)," a lumbar puncture with oligoclonal bands, and "several episodes of lesions and deficits separated by time and space." Id. Dr. Elmore determined Petitioner's "cognitive complaints" and "diffuse fatigue" were also likely due to MS. Id. Dr. Elmore observed that Petitioner first "presented more like a peripheral nerve issue" and "wonder[ed] if he had new onset CIDP at the time." Id. While this was "still possible," Dr. Elmore now thought that CIDP had been "overshadowed by" Petitioner's MS. Id. He added that Petitioner's "abrupt deterioration started after a flu shot." Id. Treatment was instituted with five days of intravenous ("IV") prednisone, followed by an oral prednisone taper. Id. Petitioner was also referred for a second opinion. Id.

On November 9, 2017, Petitioner saw neurologist Salim Chahin, M.D. Pet. Ex. 2 at 1-4. Petitioner reported a history of ataxia[13] following a febrile illness that occurred more than 30 years prior. Id. at 1. Symptoms persisted for two months, and it took one year for Petitioner to return to his normal state. Id. Petitioner "believe[d] he could have had [Epstein-Barr virus ("EBV")] encephalitis but this was never confirmed" with testing. Id. Dr. Chahin opined these "remote neurologic symptoms 33 years ago [] were attributed to encephalitis [and] could have potentially be[en] the first relapse of a demyelinating illness since he was not officially diagnosed with encephalitis." Id. at 3. Petitioner also reported a past history of foot drop after lifting heavy objects and carpal tunnel syndrome, which Dr. Chahin opined "could be explained by nerve impingement or entrapment although not all responded to treatment." Id. at 1, 3.

Regarding Petitioner's recent neurologic symptoms, Petitioner stated his symptoms began about four to six weeks after receipt of a flu vaccination in October 2016. Pet. Ex. 2 at 1. Petitioner described the symptoms as bilateral numbness in his legs that gradually ascended to his mid-tibias that worsened, and were followed by cognitive problems. Id. By the summer of 2017, Petitioner stated that he had numbness in his hands, weakness in his arms, and significant fatigue. Id. He reported that IV steroids "transiently helped the weakness in the arms" and helped with numbness in the hands and (to a lesser degree) feet. Id.

[13] Ataxia is "failure of muscular coordination" or "irregularity of muscular action." Ataxia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=4630 (last visited Dec. 6, 2024).

Dr. Chahin's neurologic examination documented Petitioner exhibited normal motor and strength. Pet. Ex. 2 at 2. Sensation was normal except for "[m]ild decreased vibration in fingers[] [and] mod[erately] at knees." Id. at 3. Reflexes were normal except trace reflexes in the Achilles tendons. Id. Petitioner had normal station and gait, but had "[s]ome trouble with [his] right foot when walking on [his] heels," "impaired" tandem walk, and negative Romberg. Id. Dr. Chahin reviewed Petitioner's MRI and CSF results and opined the results "show[ed] a typical demyelinating pattern." Id. "Given [Petitioner's] history and the published data on vaccinations and demyelinating illnesses, [Dr. Chahin] [did] not think the flu shot caused [Petitioner's] illness (which might [be] remote anyways)" and explained "vaccinations could trigger a relapse but do not actually cause the illness itself." Id. Dr. Chahin opined "[i]t is possible that [Petitioner] suffered CIDP following the vaccination," although his EMG "did not definitely show a demyelination neuropathy." Id. Dr. Chahin also questioned whether Petitioner had a "peripheral neuropathy given his prior EMG and his exam[ination], but [] wonder[ed] if [it was] an idiopathic axonal neuropathy." Id. A repeat EMG/NCS was ordered, along with a demyelinating neuropathy panel. Id. Dr. Chahin was "inclined" to diagnose Petitioner with MS "[i]f all other explanations [were] ruled out." Id.

Petitioner underwent multiple laboratory tests on November 9 and November 10, 2017. Pet. Ex. 2 at 5-6; Pet. Ex. 16 at 8-18. All tests were normal except for Petitioner's prostate-specific antigen ("PSA") level,[14] which was elevated at 4.40 (reference range 0-4.0). Pet. Ex. 16 at 16. Petitioner had a repeat EMG/NCS on November 20, 2017, which showed "evidence of mild distal axonal neuropathy." Pet. Ex. 23 at 5. No abnormalities were seen "to support a demyelinating neuropathy or CIDP." Id. Additionally, the study revealed "absent left sural [sensory nerve action potential ("SNAP")] [] suggestive of a left sural neuropathy."[15] Id.

Petitioner followed up with Dr. Elmore on December 6, 2017. Pet. Ex. 4 at 16-20. Petitioner continued to have fatigue and confusion. Id. at 16. Dr. Elmore's assessment remained clinically definite MS due to abnormal MRIs and lumbar puncture. Id. at 19. Dr. Elmore further stated

> [Petitioner] [was] concerned that his flu shot precipitated all of this. It most certainly did not cause his MS as I believe his MS was preexisting (He even had an episode that sounds like MS 30 years ago and his MRI shows a lot of chronic changes that pre-date his flu shot). It is possible that the flu shot precipitated a flare-up which many neuroimmunologist[s] believe is possible.

[14] PSA "serum levels are elevated in benign prostatic hyperplasia and prostate cancer. Measurement of PSA serum levels is used as a screening test for prostate cancer." Prostate-Specific Antigen, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=56964 (last visited Dec. 6, 2024).

[15] Sural nerve is a sensory nerve suppling the "skin on back of leg, and skin and joints on lateral side of heel and foot." Nervus Suralis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=92418 (last visited Dec. 6, 2024).

Id. Petitioner was started on Amantadine[16] for his MS. Id. Dr. Elmore opined Petitioner was permanently disabled given his MRI findings and symptoms and would not be able to return to work as a physician. Id. at 20.

On January 22, 2018, Petitioner saw Robert Bucelli, M.D., and James Giles, M.D., at the Washington University Neuromuscular Clinic for another opinion about his neuropathy in the setting of his MS or "CNS[17] demyelinating disea[s]e." Pet. Ex. 3 at 4-9. Petitioner described his clinical course:

> In October 2016, four weeks after receiving a flu shot, he developed numbness and tingling in his bilateral feet that progressed and ascended up his legs. Shortly afterwards, he developed bilateral proximal arm weakness, which waxed and waned, though overall improved to the point that it was not bothersome to him. In March 2017 he developed a sense of fatigue to accompany the arm weakness. By June 2017 he had developed a right foot drop and then presented to a neurologist's office. . . .
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> In September 2017 his arm became weak again and he was treated with [five] grams of IV methylprednisolone with marked improvement in his arm weakness and the numbness and tingling in his bilateral feet also improved. Since stopping the steroids and tapering off as an outpatient, the numbness and tingling has recurred, and he was started on gabapentin for symptomatic relief. . . .

Id. at 4. At the time of this visit, Petitioner complained of "persistent numbness and tingling in his bilateral feet without asymmetry," reported "developing numbness and tingling in the fourth and fifth digits of his left hand over the last couple of months," but he denied new weakness, bowel and bladder problems, or vision or autonomic changes. Id. at 5. Dr. Bucelli and Dr. Giles reviewed Petitioner's prior testing, including his MRIs, lumbar puncture, EMG/NCS from November 2017, and blood work. Id. at 4-5, 7.

Physical examination revealed "mild wasting of his left [first dorsal interosseous ("FDI")] muscle," "mildly slow finger tapping bilaterally," mildly diminished reflexes (1+) in his biceps, brachioradialis, and triceps bilaterally and his left ankle, and toes downgoing bilaterally. Pet. Ex. 3 at 6-7. Sensory examination showed "reduced vibration sensation in his legs," with

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[16] Amantadine "augments the release of dopamine" and is a "commonly used off-label symptomatic medication" for MS-fatigue. Amantadine Hydrochloride, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=2031 (last visited Dec. 6, 2024); F. Bethoux & the Mellen Center Professional Staff, Fatigue in the Context of MS, Cleveland Clinic, https://my.clevelandclinic.org/departments/neurological/depts/multiple-sclerosis/ms-approaches/ms-and-fatigue (last visited Dec. 6, 2024).

[17] The CNS is "the part of the nervous system consisting of the brain and spinal cord." Central Nervous System, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=111791 (last visited Dec. 6, 2024).

proprioception intact throughout and negative Romberg. Id. at 7. Lastly, Petitioner's gait was normal except for "some mild difficulty with tandem [walking]." Id.

Dr. Giles noted Petitioner's EMG/NCS "show[ed] a distal sensorimotor axonal neuropathy as well as a left sural mononeuropathy." Pet. Ex. 3 at 7. He noted Petitioner "may have an immune mediated axonal neuropathy," but both Dr. Giles and Dr. Bucelli agreed Petitioner had no demyelinating features on his electrodiagnostic testing to suggest a demyelinating neuropathy, such as CIDP. Id. at 7-8. Additional blood work was ordered as well as a repeat EMG/NCS and neuromuscular ultrasound. Id.

Neuromuscular antibody testing was normal. Pet. Ex. 3 at 10. A neuromuscular ultrasound of the left arm and left leg, performed on January 22, 2018, revealed left ulnar neuropathy at the elbow and "[n]o other abnormalities to support an inflammatory or demyelinating polyneuropathy." Id. at 16. EMG/NCS also revealed evidence of left ulnar neuropathy across the elbow. Pet. Ex. 19 at 14-17. In addition, the sural SNAP was absent on the left and normal on the right. Id. at 15. "The absent sural on the left [was] compatible with left sural neuropathy or asymmetric polyneuropathy." Id. No evidence for active denervation was noted. Id. Lastly, mild denervation in the dorsal interosseous pedis III/IV was seen, consistent with Petitioner's previous study, suggesting mild distal neuropathy. Id.

On February 19, 2018, Petitioner saw Hui Zhang, M.D., a hematologist/oncologist, for evaluation of an abnormal serum light chain ratio and mild anemia. Pet. Ex. 13 at 2-10. Dr. Zhang noted that an elevated free light chain supported the diagnosis of MS and that peer-reviewed literature showed that it was a sensitive and specific diagnostic parameter for MS. Id. at 10. Dr. Zhang ordered additional testing to rule out amyloidosis or myeloma. Id. Dr. Zhang also documented Petitioner's mild anemia was chronic since childhood and that he was being followed by a urologist for his elevated PSA. Id.

Petitioner returned to Dr. Elmore on February 21, 2018. Pet. Ex. 4 at 11-15. Dr. Elmore maintained Petitioner had "[c]linically definite MS." Id. at 14. Dr. Elmore "believe[d] [Petitioner] had MS long before he had to take his mandatory flu shot" and that the October 7, 2016 flu vaccination "could have caused a relapse of his MS." Id. Petitioner returned to Dr. Elmore on May 22, 2018. Id. at 6-10. Dr. Elmore again stated that Petitioner's MS "presented with a flu shot which could have caused an exacerbation of [Petitioner's MS]." Id. at 10. At a follow-up appointment with Dr. Elmore on July 5, 2018, Dr. Elmore stated "[Petitioner] had an exacerbation of his MS and probably an acute flare up immediately after taking a flu shot. I think his flu shot probably precipitated this. He has not had a flare up or any progression of MS for many years prior to this event." Id. at 4.

Petitioner returned to the Washington University Neuromuscular Clinic on May 21, 2018. Pet. Ex. 19 at 4-8. Dr. Bucelli and Dr. Omar Butt noted Petitioner's EMG/NCS from November 28, 2017 and January 22, 2018 "showed stable distal sensory-motor axonal neuropathy as well as a left sural mononeuropathy without any demyelinating features on electrodiagnostic testing or nerve enlargement on ultrasound. A left ulnar entrapment neuropathy was also appreciated." Id. at 4. It was also noted that Petitioner wrote a letter to Dr. Bucelli and Dr. Chahin

> detailing his strong belief that his symptoms are not necessarily related to his MS diagnosis but rather a post-immunization CIDP. He acknowledge[d] his initial symptoms were mainly numbness but add[ed] that in hindsight he also had subjective arm weakness as well. He fe[lt] his FLAIR changes seen on MRI [were] due to his history of mono-encephalitis, although he later clarifie[d] . . . that he does believe in fact he has MS. He [] repeat[ed] he feels that his CNS involvement may be related to CIDP, namely his mental fogginess. He favor[ed] this diagnosis due to his response to steroids.

Id.; see also Pet. Ex. 22 at 1-3 (letter).

On examination, Petitioner exhibited mild wasting of the FDI muscle in his left hand, but otherwise normal strength throughout; pin gradient to the level of mid-calf and mid-forearm; reduced vibration sensation in his left ankle and toe; and mildly reduced reflexes in the biceps bilaterally. Pet. Ex. 19 at 6. Petitioner had mild difficulty with tandem walking. Id. Drs. Bucelli and Butt determined that Petitioner did not have CIDP, stating "[t]here is nothing about his presentation to warrant a concern for CIDP. . . . He could have had a post-vaccination, monophasic, immune-mediated neuropathy, but this isn't CIDP." Id. at 7.

Drs. Bucelli and Butt had a lengthy discussion with Petitioner, explaining that "immune neuropathies would not result in cognitive changes" and "many of his sensory changes in the legs could simply be related to his [CNS] demyelinating disease" because he had "very little electrophysiologic evidence of large fiber neuropathy and that the only hard finding to date has been a left sural mononeuropathy of unclear etiology." Pet. Ex. 19 at 7. They recommended that Petitioner undergo ulnar release surgery to address his hand weakness, which had worsened since his last visit. Id.

On July 6, 2018, Petitioner saw Christopher Maender, M.D., an orthopedic surgeon. Pet. Ex. 18 at 3-8. Petitioner reported numbness and tingling in the fourth and fifth fingers of his left hand, which had been present for approximately one year, and was progressively increasing. Id. at 3. Assessment was left-sided cubital tunnel syndrome. Id. at 4. Petitioner requested surgery (an ulnar nerve release), which was done on August 30, 2018. Id.

Petitioner returned to Dr. Zhang for a follow-up appointment on August 20, 2018. Pet. Ex. 13 at 107-13. Petitioner reported he continued to have fatigue and mild numbness and abnormal sensation in his left hand. Id. at 107. He reported his memory, daytime sleepiness, and depression had improved. Id. Dr. Zhang reviewed Petitioner's recent bloodwork and agreed that Petitioner's elevated free light chain supported the diagnosis of MS. Id. at 11-13.

At a post-surgery follow-up examination on September 12, 2018, Petitioner's sensation had improved since surgery and physical examination noted Petitioner had near full range of motion in his left elbow, good finger strength, and normal sensation to light touch. Pet. Ex. 18 at 7.

On September 13, 2018, Petitioner underwent MRIs which were unchanged from those done in September 2017. Pet. Ex. 15 at 20-21, 27-28. On October 24, 2018, Petitioner saw Dr.

Elmore, who confirmed that Petitioner's recent MRIs did not reveal any new lesions and that Petitioner appeared stable. Id. at 8-12. Examination was normal except for slight unsteadiness. Id. at 11. Assessment was "1. Clinically definite MS. 2. Possible CIDP. 3. Gait disorder." Id.

Petitioner returned to Dr. Elmore in June 2019 and June 2020. Pet. Ex. 53 at 102-05, 113-16. Diagnosis remained clinical definite MS. Id. at 105, 116. A July 13, 2020 brain MRI[18] remained consistent with MS and was stable in appearance when compared to his previous MRI in September 2018. Id. at 109-10.

Petitioner started seeing Reuben Valenzuela, M.D., as his treating neurologist in July 2020. Pet. Ex. 53 at 91-95. Dr. Valenzuela agreed Petitioner's diagnosis was progressive MS after reviewing his clinical course and imaging studies and conducting a neurological examination. Id. at 91. On September 29, 2020, December 29, 2020, March 30, 2021, and June 29, 2021, Dr. Valenzuela documented that Petitioner remained stable with "no relapses, new neurologic symptoms[,] or progression" of his MS. Id. at 29, 56, 67, 76.

On August 17, 2021, Petitioner had MRIs of his cervical spine and brain. Pet. Ex. 53 at 19-22. Petitioner's cervical MRI revealed a chronic demyelinating plaque in the spinal cord at the C4-C5 level that was new since the prior cervical MRI done July 2020. Id. at 21-22. Brain MRI was stable and showed no new lesions or active demyelination since the July 2020 MRI. Id. at 19. Dr. Valenzuela reviewed these MRIs and agreed the brain MRI was stable and the chronic demyelinating plaque at C4-C5 "look[ed] new." Id. at 11.

During Petitioner's December 14, 2021 visit with Dr. Valenzuela, Petitioner reported "no relapses, new neurological symptoms[,] or progression." Pet. Ex. 53 at 3. Petitioner continued to report "no relapses, new neurological symptoms[,] or progression" throughout visits in 2022. Pet. Ex. 62 at 10. Repeat MRIs in 2022 remained unchanged and were stable. Id. By December 12, 2022, Dr. Valenzuela documented Petitioner was "[d]oing very well overall." Id. Petitioner stated that he had "no relapses, new neurological symptoms[,] or progression" during a March 2023 visit with Dr. Valenzuela.

No additional relevant records were filed.

3. Petitioner's Hearing Testimony and Affidavits[19]

Petitioner is a medical doctor who practiced internal medicine for 35 years before retiring in 2017. Tr. 6-7.

Petitioner received a flu vaccination on October 7, 2016 at the age of 62. Tr. 8. Prior to this vaccination, Petitioner would describe his health as "excellent;" he was not on any

[18] A cervical MRI was also conducted on this date; however, the undersigned was unable to find the report from this MRI.

[19] Petitioner provided two affidavits and testified at the entitlement hearing. Pet. Exs. 7, 26; Tr. 4.

medication and had no ongoing medical conditions. Id. He worked 40 to 50 hours per week, four days a week. Id. He was "very active;" he rode his bicycle almost daily, did yard work, traveled, and played golf. Tr. 9. He had "[n]o unexplained neurologic symptoms" at that time. Id.

However, in 1984, when he was 30, Petitioner had EBV and "became very ill" for approximately two weeks. Tr. 9. A "couple weeks" later, he "developed ataxia, was walking into walls[,] . . . [and] had some gross [] motor dysfunction." Id. He also had difficultly playing softball like he used to and had "mild slurred speech." Id. Petitioner saw a neurologist a "couple months" after symptom onset. Tr. 10. His computed tomography ("CT") was unremarkable and he believed his lumbar puncture showed pleocytosis.[20] Tr. 11. Petitioner "presumptively diagnosed [him]self with mono encephalitis," and his neurologist "agreed that [he] probably had mono encephalitis, but there was nothing definite from the studies that could say with absolute certainty." Tr. 10-11. Petitioner "[n]ever had any reemergence of any of those symptoms. They took approximately a year to resolve, and after that time [he] was neurologically intact with none of the symptoms [he] had during that episode." Tr. 11.

Then, in 2000, Petitioner was building a retaining wall at his new house when he "developed some radicular pain down [his] right leg into [his] big toe." Tr. 10. He lost his ankle reflex, had mild foot drop, and had some numbness and tingling down his right leg. Id. He attributed these symptoms to lifting a heaving object, and when he stopped working on the retaining wall, his symptoms resolved over a couple weeks and did not return. Id.

As to the more recent event, Petitioner explained that approximately three or four weeks after his flu vaccination on October 7, 2016, he began experiencing neurological symptoms he described as "extremely subtle numbness and tingling in both [of his] feet bilaterally and equally." Tr. 11-12. Petitioner was "confident" that his symptoms started in early November because he recalled telling his wife about the symptoms and she wrote them in her calendar. Tr. 12. Over the next few months, his symptoms intensified and became "more pronounced," "gradually ascend[ing] slightly." Tr. 12-13. Around December 2016 to January 2017, Petitioner developed fatigue, mental fogginess, and some mild memory issues. Tr. 13. At this time, he did not seek medical treatment and was self-diagnosing and self-treating. Id. He testified that he "had come up with a presumptive diagnosis that [he] had CIDP based on the timing of the vaccine and [his] symptoms." Id. He recalled mentioning his symptoms to his partners and nurse in January or February 2017. Id.

Petitioner saw his urologist in January 2017 for concerns of prostate cancer. Tr. 14. He did not discuss his neurologic symptoms at that visit. Id. He did not believe his neurologic symptoms were related to his symptoms or concerns of prostate cancer. Tr. 15.

His symptoms continued to worsen, prompting him to get blood work done in May 2017 and see a neurologist, Dr. Elmore, in June 2017. Tr. 15. Petitioner detailed his visits with

[20] Pleocytosis is "presence of a greater than normal number of cells in the [CSF]." Pleocytosis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=39556 (last visited Dec. 6, 2024).

medical providers since June 2017, including visits to his neurologist, MS specialists, and neuromuscular specialist, and he discussed his symptoms during those visits. See Tr. 16-29; Pet. Ex. 7 at 2-4. As of the entitlement hearing on April 2, 2024, Petitioner was experiencing symptoms that affected his daily life. Tr. 29-32.

Regarding his delay in seeking treatment until June 2017, Petitioner averred that when his symptoms initially began, they were "very subtle making [him] wonder if they were real or not." Pet. Ex. 26 at ¶ 8. But as the symptoms progressed in severity and distribution, he considered other diagnoses and "concluded [he] might have CIDP as the temporal relationship was perfect with respect to [his] vaccine and other possible causes would not be related to a vaccine as far as timing was concerned." Id. He believed he came to this conclusion in January 2017 and chose to self-monitor his condition. Id. at ¶ 9. As his symptoms continued to progress, he became more concerned and decided to then seek medical advice and obtain a diagnosis. Id. at ¶ 10. He concluded that "[f]rom [his] perspective, [he] logically followed a plan which was based on sound medical knowledge." Id.

4. Other Affidavits

a. Carole Juranek

Carole Juranek is the wife of Petitioner. Pet. Ex. 25 at ¶ 1. She described Petitioner as someone who never complains about his health. Id. Mrs. Juranek explained that she keeps detailed calendars of her family's schedule, and she looked through the calendars and her photographs to prepare her affidavit. Id. at ¶¶ 3-4.

According to Mrs. Juranek's calendar from October 2016, Petitioner received his flu vaccine on October 7, 2016. Pet. Ex. 25 at ¶ 5, Ex. A. In her November 2016 calendar, there was an entry on November 6 stating "Bob feet numbness and tingling." Id. at ¶ 6, Ex. B. Mrs. Juranek averred that she remembered Petitioner mentioned he had "slight numbness and tingling at night when he would sleep" around Election Day. Id. at ¶ 6. At the time, they "didn't think much of it," but she "thought to write it down when he mentioned it" because "it was so unusual for [Petitioner] to complain about his health." Id.

Mrs. Juranek recalled an event she and Petitioner attended on December 21, 2016 where Petitioner "mentioned his shoes were making his feet go numb" and he decided to not wear dress shoes. Pet. Ex. 25 at ¶ 7, Ex. C. She also recalled buying him shoes for Christmas in 2016 because his feet were still bothering him. Id. at ¶ 8, Ex. D.

Mrs. Juranek went back to work on January 14, 2017. Pet. Ex. 25 at ¶ 9. She recalled that in February and March 2017, she would call Petitioner at home on his days off and he would be napping, which "was very unusual for him because he was always full of energy." Id. Around this time, Petitioner's nurse, Elizabeth Loveless, told Mrs. Juranek that she had also started to notice how Petitioner seemed more fatigued. Id. at ¶ 9, Ex. E. Mrs. Juranek remembered that she and Ms. Loveless "noticed his fatigue was getting worse" in March and April 2017. Id. at ¶ 9. "Around this time, [she] remember[ed] [Petitioner] mentioning . . . he thought his symptoms were probably some kind of neuropathy caused by his flu shot . . . ." Id. at

¶ 10. "By April or May of 2017, the numbness and tingling in his feet . . . was bothering him more throughout the day." Id. at ¶ 11. In May 2017, Dr. Townsend, a colleague, ran blood work, which was normal, and Petitioner made an appointment with a neurologist, Dr. Elmore in June. Id.

b. Elizabeth Loveless

Elizabeth Loveless was Petitioner's registered nurse from October 2012 until Petitioner retired in late 2017. Pet. Ex. 27 at ¶ 1. During those five years, they worked side-by-side five days per week. Id. at ¶ 2.

She averred Petitioner's "energy level started to change [] in the Fall of 2016," although she noted she "[could not] be more specific about exactly when the changes began." Pet. Ex. 27 at ¶ 3. These changes in Petitioner continued through winter and spring, during which time she was also struggling with personal health issues. Id. Ms. Loveless described these "changes" as fatigue, which she had not seen prior. Id. at ¶ 4. Additionally, she noted Petitioner started to complain of numbness and tingling in his lower extremities, but she "[did not] remember precisely when . . . it began." Id. at ¶ 5. "[A]fter a while, maybe it was [a] few weeks or a few months, the symptoms were getting worse and he finally consulted with another physician in our office, Dr. Townsend," and had blood work done. Id.

C. Expert Reports[21]

1. Petitioner's Expert, Dr. Dr. Lawrence Steinman[22]

a. Background and Qualifications

Dr. Steinman is board certified in neurology and has practiced neurology at Stanford University for over 43 years. Pet. Ex. 28 at 1. He received his B.A. from Dartmouth College in 1968 and his M.D. from Harvard University in 1973. Pet. Ex. 67 at 1. Thereafter, he completed a surgical internship, pediatrics residency, and pediatric and adult neurology residency at Stanford University Hospital, as well as three fellowships, including one in clinical immunology. Id. Dr. Steinman is currently a Professor at Stanford University. Id. Dr. Steinman "is actively involved in patient care" and "ha[s] cared for hundreds of adults and children with various forms of neuroinflammatory diseases including [MS], [ADEM], optic neuritis, [GBS], [CIDP], transverse myelitis, inflammatory neuropathy, [and] neuromyelitis optica." Pet. Ex. 28 at 1. He has authored or co-authored over 600 publications. Pet. Ex. 67 at 5-49. Dr. Steinman has authored papers on molecular mimicry and MS, as demonstrated by his CV. See id. One of Dr. Steinman's specialties is in the area of MS, and he has received a Charcot Prize for Lifetime

[21] Although the undersigned has reviewed all of the expert reports and expert testimony, for the sake of brevity this Decision does not include every detail of the experts' opinions. Instead, the undersigned focuses on the experts' material opinions, as they relate to the relevant issues.

[22] Dr. Steinman testified at the hearing and submitted three expert reports. Tr. 4; Pet. Exs. 28-29, 56.

Achievement due to his research in MS. Pet. Ex. 28 at 2. In 2015, he was elected to the National Academy of Sciences. Id. Dr. Steinman is also a member in the National Academy of Medicine. Id.

b. Opinion

Dr. Steinman opined the flu vaccine Petitioner received in October 2016 significantly aggravated his pre-existing MS via molecular mimicry between the flu vaccine (specifically, the nucleoprotein of B/Brisbane/60/2008-like virus) and gliomedin. Pet. Ex. 28 at 1, 9, 17, 19; Tr. 44.

i. Background and Diagnosis

Dr. Steinman opined Petitioner's diagnosis is MS, which he first developed in his 30s and was then significantly aggravated in 2016, 30 years later, following a flu vaccination. Pet. Ex. 28 at 9; Tr. 69-70. He opined that Petitioner did not have CIDP. Tr. 60.

He defined MS as a CNS disease that occurs in different regions of the brain (and spinal cord). Tr. 62-63. MS has two major types: relapsing-remitting and progressive. Tr. 63-64. Dr. Steinman testified that the pathogenesis of MS was thought to be a two-stage disease, with a stage of inflammation and a stage of degeneration. Tr. 65. However, Dr. Steinman no longer believes this is accurate since inflammation continues during degeneration. Id.; see Pet. Ex. 69.[23]

Recent studies (2022) have shown that EBV, the virus that causes mononucleosis, may lead to the development of MS. Tr. 66 (citing Pet. Ex. 58;[24] Pet. Ex. 59).[25] "[M]olecular mimicry between a molecule in the [CNS] . . . could explain how [] EBV could lead to MS."[26] Tr. 67. For there to be a relapse of MS, Dr. Steinman testified that in addition to having a prior infection with EBV, there must be a "second hit," which he opined can be due to vaccination and molecular mimicry. Tr. 66-68.

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[23] Lawrence Steinman & Scott S. Zamvil, Beginning of the End of Two-Stage Theory Purporting That Inflammation Then Degeneration Explains Pathogenesis of Progressive Multiple Sclerosis, 29 Current Op. Neurology 240 (2016).

[24] Kjetil Bjornevik et al., Longitudinal Analysis Reveals High Prevalence of Epstein-Barr Virus Associated with Multiple Sclerosis, 375 Science 296 (2022).

[25] Tobias V. Lanz et al., Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 and GlialCAM, 603 Nature 321 (2022). Dr. Steinman is a named author. Lanz et al. showed that molecular mimicry between EBV nuclear antigen 1 and the CNS protein glial cell adhesion molecular provides a mechanistic link for how the EBV infection can contribute to the induction of MS. Pet. Ex. 59 at 1.

[26] According to Dr. Steinman, the initial trigger of Petitioner's MS may have been the EBV infection he had when he was 30. Pet. Ex. 28 at 9, 20.

ii. Loving Factors One, Two, and Three

With regard to Loving factor one (Petitioner's condition prior to vaccination), Dr. Steinman opined that Petitioner's neurological event in his 30s, characterized by ataxia, slurred speech, and gross motor dysfunction, "was likely the initial presentation of [MS]." Pet. Ex. 28 at 5; see also Tr. 61, 69. He further opined that the trigger of Petitioner's MS was likely infectious mononucleosis triggered by EBV infection. Pet. Ex. 28 at 20.

He testified that Petitioner's MRI showed lesions that "could have easily accounted for the ataxia and slurred speech" Petitioner experienced when he was 30. Tr. 122. He also had periventricular lesions, and lesions in the cervical and thoracic spines, which, according to Dr. Steinman, explained the gross motor dysfunction Petitioner had at 30 years of age. Tr. 122-23. However, due to their non-enhancing nature, Dr. Steinman was unable to date the lesions seen on MRI. Tr. 123. He also acknowledged that lesions can be present in the absence of noticeable signs and symptoms of MS. Tr. 124.

Dr. Steinman opined that following the event (in 1984), Petitioner's MS remained dormant for 30 years until Petitioner's flu vaccination in October 2016. Pet. Ex. 28 at 5, 9; Tr. 69-70. He opined Petitioner had no manifestations of MS over this 30-year period. Tr. 70.

However, Dr. Steinman agreed that Petitioner's neurological symptoms (foot drop, loss of ankle reflex, numbness, and tingling) in 2000 "could be attributed to [] MS" or could have been caused by Petitioner lifting heavy objects for a home improvement project. Tr. 117-18. Petitioner's first MRIs in 2017 showed lesions at T2, which Dr. Steinman agreed could be consistent with Petitioner's neurologic symptoms in 2000 and consistent with a relapse of MS. Tr. 119-20. Even though Dr. Steinman "prefer[red]" to attribute those symptoms to Petitioner's construction work on his home, as Petitioner did, based on Petitioner's testimony, he acknowledged the symptoms could have been an MS relapse, testifying that he "[could not] rule out and [] should not rule out that it could have been MS." Tr. 120, 137. Overall, whether these symptoms were attributable to MS or physical labor, his opinions were unchanged. Tr. 121.

Next, Dr. Steinman discussed Loving factors two and three, Petitioner's post-vaccination condition and whether Petitioner experienced a "significant aggravation." At the time of the October 2016 flu vaccination, Petitioner was healthy. Tr. 44. He was physically active and working four to five days per week. Tr. 69. After his October 2016 flu vaccination, Petitioner developed numbness and tingling in his feet within four weeks. Pet. Ex. 28 at 19-20; Tr. 44-45, 69-70. The numbness and tingling progressed up his legs and was followed by bilateral weakness in his arms, fatigue, and cognitive issues. Pet. Ex. 28 at 19; Tr. 69-70. Because Petitioner had no symptoms attributable to MS prior to vaccination, and began experiencing MS-related symptoms within four weeks of vaccination, Dr. Steinman concluded Petitioner experienced a significant aggravation[27] of his MS following his October 2016 flu vaccination. Pet. Ex. 28 at 20; Tr. 70.

[27] Dr. Steinman testified that there was not a difference between a relapse of MS and a significant aggravation of MS, "call[ing] a relapse a significant aggravation." Tr. 68.

Dr. Steinman disagreed with Dr. Piquet's opinion that Petitioner's symptoms reflected an "expected evolution and progression of long-standing MS" and therefore inconsistent with a significant aggravation. Tr. 70-71; Pet. Ex. 29 at 8-9. Dr. Steinman opined "there is no natural course" and that Petitioner's course was "not uncommon" when compared to other Vaccine Program cases Dr. Steinman has previously been involved with. Tr. 70-71.

In support of her opinion that Petitioner did not experience a significant aggravation of his MS, Dr. Piquet noted Petitioner's 2017 MRIs did not show active lesions. Tr. 71. Dr. Steinman agreed none of Petitioner's MRIs showed enhanced lesions. Tr. 123-24. He countered that the MRIs showed lesions in his spinal cord and brain that "may have been enhancing early on," but Petitioner did not have an MRI around the time of onset when Dr. Steinman asserted the lesions were enhancing. Tr. 71-72. Further, Dr. Steinman was unable to date the lesions seen on MRI due to their non-enhancing nature. Tr. 123.

Dr. Steinman concluded that because Petitioner's MS was "quiescent for 30 years and that numbness, fatigue[,] and cognitive changes were all noted only after the [flu] immunization, those findings in themselves all represent significant aggravation." Pet. Ex. 29 at 8. "[T]o have MS remain quiescent for [three] decades and then come on with these new findings makes it far more likely to [Dr. Steinman] that there was 'significant aggravation' induced by the flu vaccine" as it is "exceptionally rare" for MS to remain dormant for 30 years or more. Id. at 9; Tr. 67.

iii. Loving Factor Four/Althen Prong One

Dr. Steinman posited that the flu vaccine can cause a significant aggravation of MS via molecular mimicry due to homology between Petitioner's flu vaccine (here, the nucleoprotein of B/Brisbane/60/2008-like virus)[28] and gliomedin. Pet. Ex. 28 at 9-10.

First, Dr. Steinman discussed gliomedin and its importance to his theory. Dr. Steinman explained that gliomedin is a protein found in the central and peripheral nervous systems, which he opined is "known to be attacked in [MS]." Tr. 75, 184-86; see also Pet. Ex. 36 at 1;[29] Pet. Ex. 37 at 1-2 (supplemental figures of Pet. Ex. 36). According to Dr. Steinman, gliomedin is "expressed on axons at the node of Ranvier" in the CNS that works as "the binding partner of Neurofascin-186" ("NF186"), which is also targeted in inflammatory diseases seen in the CNS. Pet. Ex. 28 at 9-10, 16; see also Tr. 194.

[28] For the other flu virus strains contained in the flu vaccines for 2016-2017, see Pet. Ex. 42.

[29] Yael Eshed et al., Gliomedin Mediates Schwann Cell-Axon Interaction and the Molecular Assembly of the Nodes of Ranvier, 47 Neuron 215 (2005).

In support of his opinion that gliomedin is expressed in the CNS, Dr. Steinman cited a study by Eshed et al. See Pet. Exs. 36-37. It identifies gliomedin as "a glial ligand[30] for neurofascin." Pet. Ex. 36 at 1. However, the authors found that the role of gliomedin in the assembly of the nodes of Ranvier was limited to the peripheral nervous system ("PNS"). Id. at 11. While the article supports Dr. Steinman's statements that gliomedin is "expressed on axons at the node of Ranvier" and is a "binding partner of [NF186]," this occurs in the context of the PNS, not the CNS.

The supplement related to the study does state that there was "[e]xpression of [g]liomedin mRNA in the rat sciatic nerve and brain." Pet. Ex. 37 at 1. Throughout the paper, however, the authors make a distinction between the PNS and the CNS, noting that the role of gliomedin is limited to the PNS. For example, they state that their "results suggest that Schwann cell-axon interactions mediated by gliomedin trigger the molecular assembly of the nodes of Ranvier in the PNS." Pet. Ex. 36 at 2. "Direct comparison between the sciatic nerve and the brain showed that the gliomedin transcript is much more abundant in the PNS than in the CNS." Id. at 3. "In contrast, gliomedin was not detected at the nodes of Ranvier in the CNS." Id. The authors summarized that their "results demonstrate[d] that gliomedin is a novel glial component of the nodes of Ranvier in the PNS." Id. "Taken together, [their] findings suggest[ed] that gliomedin acts as a local glial cue, which triggers the assembly of the nodes of Ranvier in the PNS." Id. at 11. Further, Eshed et al. explained that "[d]ifferent mechanisms may operate in the CNS, where nodal clustering requires the presence of oligodendrocytes." Id. at 13. Thus, the study does not support a role for gliomedin in the CNS, at least as it relates to Dr. Steinman's opinion, and its role in the pathogenesis of MS.

Regarding the reference to gliomedin RNA being expressed in the rat sciatic nerve and brain, Dr. Fujinami testified that this only "shows the presence of very minute amounts of RNA" which "doesn't mean protein." Tr. 168. Dr. Fujinami concluded that RNA does not equate to protein. Tr. 169. Dr. Steinman disagreed, stating "RNA leads to protein." Tr. 182. He reiterated his opinion that gliomedin is expressed in the spinal cord and brain. Tr. 185.

The next paper Dr. Steinman cited in support of gliomedin was authored by Notturno et al.[31] Pet. Ex. 41. It described gliomedin as a "type II transmembrane collagen[]" that "is localized at the Schwann cell microvilli that contact the node of Ranvier," that is a "ligand for NF186." Id. at 1; see also Tr. 89-90. The authors stated that NF186 is "a neuronal protein exposed on the axon surface at the nodes of Ranvier." Pet. Ex. 41 at 1. Neurofascins have been identified as "possible targets of autoantibodies in a small number of patients with [MS]." Id. at 4. However, the focus in Notturno et al. was not MS; Notturno et al. studied autoantibodies to

[30] A ligand is a "molecule that binds to another molecule, used especially to refer to a small molecule that binds specifically to a larger molecule, e.g., an antigen binding to an antibody, a hormone or neurotransmitter binding to a receptor, or a substrate or allosteric effector binding to an enzyme." Ligand, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=28261 (last visited Dec. 6, 2024).

[31] Francesca Notturno et al., Autoantibodies to Neurofascin-186 and Gliomedin in Multifocal Motor Neuropathy, 276 J. Neuroimmunology 207 (2014).

NF186 and gliomedin in patients with multifocal motor neuropathy ("MMN"), a "slowly progressive neuropathy, presenting with asymmetrical, predominantly distal limb weakness without sensory loss." Id. at 1. While they found that antibodies to NF186 and gliomedin may contribute to "motor nerve conduction failure and muscle weakness" in patients with MMN, this was in the context of the PNS and not the CNS. Id. at 5.[32] Dr. Steinman acknowledged that the Notturno paper referred to gliomedin in the PNS. Tr. 185.

In response to the opinion by Respondent's expert, Dr. Fujinami, that gliomedin was not present in the CNS, Dr. Steinman disagreed, but he "wish[ed] there were more data," stating that he was "constrained by what's available."[33] Tr. 186.

Regarding NF186 and MS, Dr. Steinman cited Mathey et al.,[34] who identified NF186 autoantibodies in MS patients. Pet. Ex. 39 at 1. In their animal model, the researchers showed that "antibodies to neurofascin selectively targeted nodes of Ranvier, resulting in deposition of complement, axonal injury, and disease exacerbation," suggesting that these antibodies may exacerbate or accelerate disease progression. Id. Specifically, they demonstrated that in an experimental autoimmune encephalomyelitis ("EAE") model, which is an animal model of MS, antibodies bind to NF186 at the node of Ranvier to initiate axonal injury in the CNS and exacerbated clinical disease in a subset of MS patients. Id. at 7-8.

Another paper cited by Dr. Steinman is Howell et al.,[35] who determined NF186 was a key component "in the assembly of nodes of Ranvier" that is "vital to successful [] nerve transmission in central and peripheral nerves." Pet. Ex. 38 at 10; see also Tr. 88. These papers did not discuss gliomedin or its role is disease pathogenesis. However, the authors did note "ongoing disruption to the axonal-oligodendrocyte complex"[36] in new and established MS lesions, "resulting in the destruction of the [NF186] nodal complex vital to successful fast neurotransmission in the CNS." Pet. Ex. 38 at 1.

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[32] For specific results of the research done by Notturno et al., see Pet. Ex. 41 at 5.

[33] After the hearing, Petitioner filed an excerpt from the Human Protein Atlas, showing that gliomedin RNA was expressed in the cerebral cortex, with smaller amounts expressed in connective and soft tissue and elsewhere, and low amounts of gliomedin protein was expressed in the cerebral cortex, caudate, colon, and high amounts were expressed in soft tissue. Pet. Ex. 77 at 1-4 (GLDN, Hum. Protein Atlas, https://www.proteinatlas.org/ENSG00000186417-GLDN/tissue (last visited May 3, 2024)).

[34] Emily K. Mathey et al., Neurofascin As a Novel Target for Autoantibody-Mediated Axonal Injury, 204 J. Experimental Med. 2363 (2007).

[35] O.W. Howell et al., Disruption of Neurofascin Localization Reveals Early Changes Preceding Demyelination and Remyelination in Multiple Sclerosis, 129 Brain 3173 (2006).

[36] "Oligodendrocyte derived myelin enwraps axons in the CNS allowing the rapid propagation of action potentials from node to node by saltatory conduction." Pet. Ex. 38 at 1.

Next, Dr. Steinman described molecular mimicry generally. Pet. Ex. 28 at 10-11. Citing to a 1993 paper[37] he authored, Dr. Steinman explained that when a foreign antigen (here, from the vaccine) resembles an antigen in the body (which Dr. Steinman suggests is gliomedin), self-antigens are attacked. Id. at 10 (citing Pet. Ex. 43 at 5). He cited Fujinami et al.[38] who stated "[m]olecular mimicry represents a shared immunologic epitope with a microbe and the host." Id. (quoting Pet. Ex. 44 at 1). Fujinami et al. hypothesized that this shared homology leads to an autoimmune disease when the cross-reaction occurs at a "'disease-related' epitope." Id. (quoting Pet. Ex. 44 at 2). Dr. Steinman testified that here, the "disease-related epitopes" are the components of the flu vaccine and gliomedin. Tr. 84-85.

Dr. Steinman opined that "[a]n autoimmune response can begin even if the molecular mimicry is not quite exact." Pet. Ex. 28 at 11 (quoting Pet. Ex. 43 at 5). For support, he cited studies from Gautam et al.[39] for the proposition that autoimmune encephalomyelitis could be induced with only five amino acids identical to myelin basic protein, out of short sequences of 10 amino acids. Id. at 11-12 (citing Pet. Exs. 46-48). One Gautam et al. study was able to induce clinical paralysis in EAE, the model of ADEM and "a very good model for MS," when five amino acids were identical between the virus and myelin basic protein and only three of the five were consecutive. Pet. Ex. 48 at 5, 5 fig.4; Tr. 80. Another Gautam et al. study determined "a six-amino acid peptide with only five native residues can induce EAE." Pet. Ex. 47 at 5. And a third study from Gautam et al. determined a minimum of four amino acids can stimulate inflammation and EAE was induced when five of 11 amino acids were identical. Pet. Ex. 46 at 1-3, 2 fig.1, 3 tbl.1. Dr. Steinman also cited Root-Bernstein,[40] who used the same criteria to find mimicry occurs in certain scenarios. Pet. Ex. 28 at 12, 15 (citing Pet. Ex. 49 at 1 ("Similarities were considered to be significant if a sequence contained at least [five] identical amino acids in 10.")).

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[37] Lawrence Steinman, Autoimmune Disease, 269 Sci. Am. 106 (1993).

[38] Robert S. Fujinami et al., Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease, 19 Clinical Microbiology Revs. 80 (2006).

[39] Anand M. Gautam et al., A Polyalanine Peptide with Only Five Native Myelin Basic Protein Residues Induces Autoimmune Encephalomyelitis, 176 J. Experimental Med. 605 (1992); Anand M. Gautam et al., Minimum Structural Requirements for Peptide Presentation by Major Histocompatibility Complex Class II Molecules: Implications in Induction of Autoimmunity, 91 Immunology 767 (1994); Anand M. Gautam et al., A Viral Peptide with Limited Homology to a Self Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis, 161 J. Immunology 60 (1998). Dr. Steinman is a named author in all these papers.

[40] Robert Root-Bernstein, Rethinking Molecular Mimicry in Rheumatic Heart Disease and Autoimmune Myocarditis: Laminin, Collagen IV, CAR, and B1AR As Initial Targets of Disease, 2 Frontiers Pediatrics 1 (2014).

Dr. Steinman conducted a BLAST[41] search to determine whether there was homology between NF186 or gliomedin and Petitioner's flu vaccine. Pet. Ex. 28 at 16. He found a sequence[42] ("KSK sequence") that "ha[d] [six] of [nine] identical amino acids shared between the nucleoprotein of the Brisbane B [flu] B virus in [Petitioner's] flu vaccine and gliomedin," five of which were consecutive. Id. at 17; Tr. 94. And at the hearing, Dr. Steinman noted another sequence that began with those same five consecutive amino acids (GNAFI), resulting in only five identical amino acids. Tr. 94; see Pet. Ex. 28 at 17. Dr. Steinman opined that "[t]his degree of homology is sufficient" based on the studies from Gautam et al. and Root-Bernstein. Pet. Ex. 28 at 17 (citing Pet. Exs. 46-49).

Following his BLAST search, Dr. Steinman used the Immune Epitope Database ("IEDB")[43] and Alignment Resource to determine whether this mimic has been described in humans. Pet. Ex. 28 at 18-19; Tr. 97-98. He found the mimic has been studied[44] and shown to bind to a human leukocyte antigen ("HLA") molecule, which "is critical for induction of T cell responses and for T cells to provide help to B cells to make antibodies." Pet. Ex. 28 at 19. Dr. Steinman did not suggest that the mimic caused or worsened an autoimmune disease.

The IEDB result provided by Dr. Steinman did not match his KSK sequence, and instead used "GNAFIGKKMFQI." Tr. 107; see Pet. Ex. 28 at 19. When asked about this difference at the hearing, Dr. Steinman testified that the difference was immaterial to his theory since all his sequences contain "GNAFI," which is still five identical and consecutive amino acids. Tr. 107. Additionally, when questioned why Dr. Fujinami did not get the same IEDB results, Dr. Steinman hypothesized that he used a wider net. Tr. 129-30 ("Maybe I just used a wide enough net . . . .").

Dr. Fujinami noted Dr. Steinman's sequence (including GNAFI) is present in all flu vaccines and questioned why this particular flu vaccine could cause a significant aggravation of MS. Resp. Ex. E at 1; see also Tr. 145-46. In response, Dr. Steinman appeared to agree that the sequence GNAFI is in all flu vaccines, stating "[t]he issue here is not that the molecular mimic is present in all seasonal [flu] vaccines." Pet. Ex. 56 at 1. Dr. Steinman explained that the issue is

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[41] A BLAST (Basic Local Alignment Search Tool) search "finds regions of similarity between biological sequences. The program compares nucleotide or protein sequences to sequence databases and calculates the statistical significance." BLAST, https://blast.ncbi.nlm.nih.gov/Blast.cgi (last visited Dec. 6, 2024).

[42] The sequence is "KSKAGNAFI" for gliomedin and "KKTSGNAFI" for the nucleoprotein. Pet. Ex. 28 at 17.

[43] The IEDB "catalogs experimental data on antibody and T cell epitopes studied in humans and other animal species in the context of infectious disease, allergy, autoimmunity[,] and transplantation. The IEDB also hosts epitope prediction and analysis tools . . . ." IEDB, https://www.iedb.org/home_v3.php (last visited Dec. 6, 2024).

[44] See Pet. Ex. 75 (Marios Koutsakos et al., Human CD8+ T Cell Cross-Reactivity Across Influenza A, C and C Viruses, 20 Nature Immunology 613 (2019)).

"the amount of [nucleoprotein] is not regulated and . . . the content of [nucleoprotein] varies considerably in different vaccines, and therefore might vary considerably from year to year."[45] Id. at 1. Thus, he asserted the amount of nucleoprotein in the vaccine was "too much" and that "too much [nucleoprotein]" would cause an exacerbation of MS. Id. at 1, 3. Of note, the content of nucleoprotein is not known for the particular vaccine at issue here. To support his assertion that the amount of nucleoprotein is important, he discussed Kappos et al.[46] and Bielekova et al.[47] Id. at 2-3 (citing Resp. Ex. E, Tab 3; Pet. Ex. 57); Tr. 103-05.

In Kappos et al. (Dr. Steinman was a senior author), MS patients were injected weekly with an altered peptide ligand ("APL") of myelin basic protein (5 milligrams ("mg"), 20 mg, or 50 mg) or a placebo to determine whether APL could confer protection against relapse or new enhancing lesions. Resp. Ex. E, Tab 3 at 1-2. The authors found "no substantial difference in the frequency . . . or the number . . . of relapses" between the groups. Id. However, the trial was suspended after 9% of patients experienced a hypersensitivity reaction. Id. at 1. Dr. Steinman acknowledged that hypersensitivity reactions do not equate to MS exacerbations. Tr. 105, 116. He cited this study because the patients who experienced hypersensitivity reactions received

[45] Dr. Steinman cited a study from Koroleva et al., showing "detectable quantities" of nucleoprotein from flu A and B viruses in the vaccines studied and "some variability" in the "viral proteins in vaccines made in separate vaccine seasons." Pet. Ex. 51 at 1, 7 (Marina Koroleva et al., Heterologous Viral Protein Interactions Within Licensed Seasonal Influenza Virus Vaccines, 5 NPJ Vaccines 1 (2020)). He also cited a paper by Ahmed et al. that described the association between a sleep disorder (narcolepsy) and the Pandemrix vaccine manufactured in 2009/2010, where "greater quantities" of nucleoprotein were detected in that flu vaccine as compared to other vaccines. Pet. Ex. 52 at 1, 5 (Syed Sohail Ahmed et al., Antibodies to Influenza Nucleoprotein Cross-React with Human Hypocretin Receptor 2, 7 Sci. Translational Med. 1 (2015)). The authors stated that the "differences in vaccine [nucleoprotein] content and respective immune response may explain the association of narcolepsy with the Pandemrix-vaccinated subjects." Id. at 5. The mechanism by which this finding may have played a causal role related to narcolepsy is beyond the scope of this decision. See id. at 7-8. Further, narcolepsy and MS do not appear to share the same pathogenesis. And Dr. Steinman did not provide evidence to show that the vaccine at issue here had a greater quantity of flu nucleoprotein or explain how such a finding would validate his theory.

[46] Ludwig Kappos et al., Induction of a Non-encephalitogenic Tyle 2 T Helper Cell Autoimmune Response in Multiple Sclerosis After Administration of an Altered Peptide Ligand in a Placebo-Controlled, Randomized Phase II Trial, 6 Nature Med. 1176 (2000). Dr. Steinman is a named author.

[47] Bibiana Bielekova et al., Encephalitogenic Potential of the Myelin Basic Protein Peptide (Amino Acids 83-99) in Multiple Sclerosis: Results of a Phase II Clinical Trial with an Altered Peptide Ligand, 6 Nature Med. 1167 (2000).

varying amounts of injections prior to their hypersensitivity reactions.[48] Pet. Ex. 56 at 2 (citing Resp. Ex. E, Tab 3 at 3 tbl.2). "Most of the reactions occur[ed] after more than 10 injections of the [APL]." Resp. Ex. E, Tab 3 at 2. The issue of quantity of nucleoprotein as it relates to the causal mechanism of molecular mimicry was not discussed.

In Bielekova et al., 24 MS patients were also injected weekly with an APL of myelin basic protein for the purposes of immunotherapy treatment. Pet. Ex. 57 at 1. Due to adverse events, the dose was decreased (50 mg weekly to 5 mg). Id. at 1, 7. The trial was then halted when one patient, who was enrolled in the lower-dose protocol, experienced an exacerbation that was considered treatment-related. Id. Dr. Steinman opined that the difference in dosage produced a different reaction as compared to Kappos et al.—in Bielekova et al., there was a worsening of MS. Tr. 104. However, it is not clear how this article supports Dr. Steinman's opinion that the amount of nucleoprotein is significant since the patient who received the lower dose regimen had an exacerbation. Further, it does not appear that outcomes were dose determinative, or alternatively, that an analysis was performed to determine whether dose amount was a factor that contributed to an adverse reaction. Overall, it does not appear that this article supports Dr. Steinman's opinion that the amount of nucleoprotein is a determinative factor.

Contrary to Dr. Fujinami, Dr. Steinman opined an unadjuvanted vaccine can trigger autoimmune disease via molecular mimicry. Tr. 187-89. He again cited Kappos et al. and Bielekova et al. for support since adjuvants were not included in either study and "unwanted immune reactions with molecular mimics" occurred in both. Tr. 105, 187-89. However, in Kappos et al., the "unwanted immune reaction" was a hypersensitivity reaction that Dr. Steinman agreed was not an exacerbation of MS. Tr. 105, 116. And in Bielekova et al., the authors stated that disease exacerbation "could be linked to an APL-induced expansion of T cells specific for [myelin basic protein]." Pet. Ex. 57 at 6. "As for the mode of action of APL," the authors discussed several different mechanisms, but Dr. Steinman did not explain how these mechanisms were consistent with his proffered mechanism of molecular mimicry. Id. at 6-7.

Dr. Steinman concluded that his BLAST search, IEDB search, and the literature (specifically, the articles from Gautam et al. and Root-Bernstein) revealed "molecular mimics in the [flu vaccine] received by [P]etitioner that could aggravate [MS]." Pet. Ex. 28 at 19.

In addition to the literature discussed above, Dr. Steinman also addressed Dr. Fujinami's literature reporting a lack of association between the flu vaccine and MS exacerbations. Miller et al.[49] examined whether flu vaccines should be administered to MS patients. Resp. Ex. A, Tab 5 at 1. In their study, patients with relapsing-remitting MS received a flu vaccine (49) or a placebo (54). Id. at 1-2. Patients were followed for six months, with examinations at four weeks and six

[48] The hypersensitivity symptoms "were self-limiting and usually resolved in [two] hours" and included itching, paresthesias, rash, shortness of breath, nausea, abdominal pain, hives, one episode of hypotension, and one episode of syncope (fainting). Resp. Ex. E, Tab 3 at 2.

[49] A.E. Miller et al., A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Influenza Immunization in Multiple Sclerosis, 48 Neurology 312 (1997).

months and telephone calls at one week and three months. Id. at 2. In the first four weeks, three vaccine patients and two placebo patients experienced MS exacerbations. Id. Over six months, vaccine patients experienced 11 disease flares and placebo patients experienced six.[50] Id. The authors determined these differences were not statistically significant and that the vaccine was safe to administer to MS patients because "it is not associated with an increased risk of exacerbation." Id. Dr. Steinman opined this article was not relevant because the flu vaccines studied in Miller et al. were from 1993 and did not include the Brisbane flu B strain relevant here. Tr. 102. Dr. Steinman also opined that while epidemiological studies are important, they do not speak to rare adverse events, or allow us to conclude that flu vaccines are "without any risk." Id.

When asked about more recent studies that have examined whether there is an association between flu vaccines and MS relapses, Dr. Steinman cited a 2016 article by Mailand and Frederiksen.[51] Tr. 131 (citing Resp. Ex. A, Tab 4). Mailand and Frederiksen conducted a literature review and identified 14 studies that examined the risk of relapse of MS following flu vaccination. Resp. Ex. A, Tab 4 at 2, 4-5 tbl.2. One study reported an increase in relapse three weeks after vaccination; however, the authors determined this study "lack[ed] statistical power, since it [was] based on only 18 patients."[52] Id. at 2, 13. The remaining studies did not find an increased risk of relapse after the seasonal flu or H1N1 vaccinations.[53] Id. at 2. The authors opined there is "no association" between the flu vaccine or H1N1 vaccine and MS relapse. Id. at 13. When asked whether he was aware of any recent studies about the risk of MS relapse after vaccination, Dr. Steinman agreed there is "no epidemiologic evidence" showing that there is an increased risk of MS relapse after receipt of the flu vaccination. Tr. 131.

iv. Loving Factor Five/Althen Prong Two

Dr. Steinman opined Petitioner's October 2016 flu vaccine was the "second hit" that significantly aggravated his pre-existing MS. Pet. Ex. 28 at 1, 9; Tr. 44, 68.

As a framework for offering opinions about a logical sequence of cause and effect, Dr. Steinman first summarized his view of Petitioner's clinical course. Pet. Ex. 28 at 19-20. Thirty

[50] The number of patients in each group that suffered relapses was not specified.

[51] Mia Topsøe Mailand & Jette Lautrup Frederiksen, Vaccines and Multiple Sclerosis: A Systematic Review, 264 J. Neurology 1035 (2017). This article was also cited as Resp. Ex. E, Tab 4 and Resp. Ex. F, Tab 2.

[52] This study was conducted in the UK and was not filed. See Resp. Ex. A, Tab 4 at 4 tbl.2 (citing Nuala McNicholas & Jeremy Chataway, Relapse Risk in Patients with Multiple Sclerosis After H1N1 Vaccination, with or Without Seasonal Influenza Vaccination, 258 J. Neurology 1545 (2011), https://pubmed.ncbi.nlm.nih.gov/21336784/).

[53] Miller et al. was one of the studies included in Mailand and Frederiksen. See Resp. Ex. A, Tab 4 at 5 tbl.2.

years prior to the flu vaccination at issue here, Petitioner developed MS. Tr. 101. Over the next 30 years, his MS remained clinically dormant. Id. Then, Petitioner received a flu vaccine on October 7, 2016, and around three to four weeks later, developed bilateral numbness and tingling in his feet. Id. at 19; Tr. 44-45. The numbness and tingling progressed, ascending in his legs. Pet. Ex. 28 at 19. He then developed bilateral weakness in his arms that waxed and waned, though it was "not bothersome." Pet. Ex. 28 at 19. In March 2017, he developed fatigue and by June 2017 he had right foot drop. Id. Petitioner presented to a neurologist in June 2017, after which he obtained testing and saw various specialists which led to his diagnosis of MS. Id.; Tr. 47-60. During this time, his symptoms continued to worsen and he developed cognitive issues (forgetfulness and difficulty concentrating). Tr. 53.

Dr. Steinman agreed with Petitioner's treating physicians' assessments. Tr. 61-62. He also opined that Petitioner's treating physicians supported the idea that there was a connection between his flu vaccination and worsening of his MS. Tr. 111.

Next, Dr. Steinman described how he believed Petitioner's flu vaccine caused a significant aggravation of MS. Tr. 127. He testified that Petitioner's immune system responded to the contents of the vaccine, specifically the "region of similarity with gliomedin, and therefore, his immune system start[ed] an attack against myelin both in the [CNS] and[] [PNS]." Id. The flu vaccine was administered in his arm, travelled to the regional lymph nodes, where T-cells and antibodies are located. Tr. 128. He further opined that the T cells crossed the blood-brain barrier and began to attack gliomedin in the CNS and PNS (evidenced by his axonal neuropathy). Id. According to Dr. Steinman, gliomedin is in the node of Ranvier in the CNS and PNS, which "is very close to the myelin," and because of the bystander effect, the myelin sustains collateral damage. Tr. 128-29.

Because Dr. Steinman's sequence (GNAFI) is present in all flu vaccines, Dr. Fujinami questioned why Petitioner's previous flu vaccines that he received yearly for work did not significantly aggravate his MS previously. Resp. Ex. E at 1; see also Tr. 145-46. In response, Dr. Steinman hypothesized that the amount of nucleoprotein in this particular flu vaccine was "too much," stating that "all it would and could take to get an exacerbation of MS would be for [Petitioner's] vaccine to contain 'too much [nucleoprotein,]' given at too many identical weekly doses." Pet. Ex. 56 at 1, 3; see also Tr. 106 (noting the amount of nucleoprotein "could be" important). However, as Dr. Steinman acknowledged, the amount of nucleoprotein in the vaccine Petitioner received is not known. Pet. Ex. 56 at 1.

Dr. Steinman opined there was no other cause for Petitioner's significant aggravation other than his flu vaccine. Tr. 69, 110. Petitioner did not have diarrhea or another illness. Id. He was physically active and worked four to five days per week. Tr. 69. Various antibodies were tested by the neuromuscular specialist in January 2018, all of which were negative, although Petitioner was not tested for antibodies to gliomedin. Tr. 75.

He testified that it is "exceptionally rare" for MS to remain dormant for 30 years or more. Tr. 67. Dr. Steinman opined that if it were not for his flu vaccine in October 2016, Petitioner's MS would have remained dormant. Tr. 110.

v. Loving Factor Six/Althen Prong Three

Dr. Steinman opined Petitioner's onset of his significant aggravation of his MS was characterized by numbness and tingling in his lower extremities that began three to four weeks after his October 2016 flu vaccination. Pet. Ex. 28 at 20; Tr. 44-45, 60. He gave three reasons why this timing was medically appropriate.

First, according to Dr. Steinman, this time frame is consistent with an adaptive immune response. Tr. 112-13. In support, he cited to the 2012 Institute of Medicine ("IOM") report.[54] Id.

Next, Dr. Steinman opined that onset is consistent with what is seen in PNS neuroinflammation, citing Schonberger et al.[55] for support. Pet. Ex. 28 at 20 (citing Pet. Ex. 50). Schonberger et al. found "[t]he period of increased risk [of GBS post-flu vaccination] was concentrated primarily within the [five]-week period after vaccination, although it lasted [] approximately [nine] or 10 weeks." Pet. Ex. 50 at 1. Schonberger et al. did not discuss MS, a CNS disease, and instead focused on GBS, a PNS disease. See id.

Dr. Steinman also cited to the package insert for flu vaccines, which warns against vaccination if a patient has had GBS within the prior six weeks.[56] Tr. 111. Again, GBS is a PNS disease. Dr. Steinman did testify that the package insert issued a similar warning relative to MS.

At the hearing, Dr. Steinman noted the subjects in Miller et al. were examined at four weeks and six months and contacted by telephone at one week and three months. Tr. 113-14 (citing Resp. Ex. A, Tab 5 at 2). Regarding the first examination at four weeks, Dr. Steinman opined this timing "fits" with Schonberger et al. Tr. 114. However, Dr. Steinman did not acknowledge the fact that Miller et al. reported "[t]he mean time of onset of relapse after flu vaccine (91.5 days) exceeded that for placebo patients (55.3 days)," and that the authors concluded that this time frame "further substantiat[ed] the lack of association between flu vaccine and MS exacerbations." Resp. Ex. A, Tab 5 at 2.

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[54] Inst. of Med., Adverse Effects of Vaccines: Evidence and Causality (Kathleen Stratton et al. eds., 2012). The chapter Dr. Steinman referred to at the entitlement hearing was not filed, although the undersigned is familiar with it. See Pet. Ex. 63.

[55] Lawrence B. Schonberger et al., Guillain-Barre Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-1997, 110 Am. J. Epidemiology (1979).

[56] Petitioner did not file the package insert for the flu vaccination at issue herein.

2. Respondent's Expert, Dr. Robert Fujinami, Ph.D.[57]

a. Background and Qualifications

In 1977, Dr. Fujinami received his Ph.D. in immunology-microbiology from Northwestern University. Resp. Ex. B at 1. He worked at the Scripps Clinic and Research Foundation in the Department of Immunopathology from 1977 to 1985. Id. While at Scripps, he and Dr. Michael Oldstone were the first to introduce the concept of molecular mimicry related to viruses and autoimmunity. Resp. Ex. A at 1. Thereafter, he was an Associate Professor in the Department of Pathology at the University of California, San Diego where, he "studied virus triggers for autoimmune disease and demyelinating diseases caused by autoimmune mechanisms and viruses." Id.; see also Resp. Ex. D at 1. In 1990, he moved to the University of Utah School of Medicine to teach in the neurology and pathology departments. Resp. Ex. D at 1. As of the time of the hearing, he was retired but remained professor emeritus in the pathology department. Tr. 140. Throughout his career, he studied "viral-host interactions" and their role in causing nervous system disease. Resp. Ex. A at 1. Dr. Fujinami has won numerous awards, has held numerous editorial and administrative positions, and has authored or co-authored over 400 publications. Resp. Ex. D at 1-7, 20-52. He also has relevant experience in viral infections, vaccines, and autoimmune diseases. Resp. Ex. A at 2.

b. Opinion

Dr. Fujinami focused his opinions on Dr. Steinman's opinions based on molecular mimicry between nucleoprotein in the Brisbane flu B virus vaccine and gliomedin, and the question of whether this causal mechanism can significantly aggravate MS and did significantly aggravate Petitioner's MS. See Resp. Exs. A, E, G.

i. Loving Factor Four/Althen Prong One

First, Dr. Fujinami disagreed that gliomedin is present in the CNS. Tr. 144, 146, 167-171, 177. He agreed with Dr. Steinman that gliomedin is a protein found at the nodes of Ranvier made by Schwann cells, which are cells that myelinate peripheral nerve myelin. Tr. 144. But he was firm in opining that gliomedin is not produced in the CNS. Tr. 144, 146, 171. And he disputed Dr. Steinman's conclusion that Eshed et al. showed gliomedin in the CNS, noting the research did not detect gliomedin at the nodes of Ranvier in the CNS. Tr. 167-70 (citing Pet. Ex. 36 at 3, 5 fig.K). Additionally, he explained that the supplemental figure in Eshed et al. showed gliomedin only in the PNS and it was not expressed in the brain or spinal cord (CNS). Tr. 168-70 (citing Pet. Ex. 37). Further, he conducted a PubMed[58] search for gliomedin in the CNS, and

[57] Dr. Fujinami testified at the hearing and submitted three expert reports. Tr. 4; Resp. Exs. A, E, G.

[58] "PubMed is a free resource supporting the search and retrieval of biomedical and life sciences literature . . . . The PubMed database contains more than 37 million citations and abstracts of biomedical literature." Nat'l Libr. Med., Nat'l Ctr. for Biotechnology Info., PubMed Overview, https://pubmed.ncbi.nlm.nih.gov/about/ (last visited Dec. 6, 2024).

did not find any articles on point. Tr. 171. He opined that because gliomedin is not found in the CNS, homology based on gliomedin is not a relevant theory applicable to a claim of significant aggravation of MS. Tr. 146.

According to Dr. Fujinami, there is another protein that is the counterpart to gliomedin in the CNS. Tr. 170-71. After the hearing, Dr. Fujinami filed two papers that identified the counterparts to gliomedin in the CNS as oligodendrocytic proteins, brevican, and several other proteins. See Resp. Ex. I at 2;[59] Resp. Ex. H at 1 (noting "[g]liomedin . . . at PNS and brevican at CNS nodes").[60]

In addition to disputing the presence of gliomedin in the CNS, Dr. Fujinami criticized Petitioner's reliance on molecular mimicry. Resp. Ex. A at 5. Dr. Fujinami defined molecular mimicry as the "sharing of amino acids or immunologic epitopes between a microbe and the host." Tr. 143. He cited the 2012 IOM report that examined adverse events for which molecular mimicry has been hypothesized, including CNS demyelinating diseases, like MS, but he noted that "molecular mimicry was not confirmed to be a mechanism leading to the development of the adverse events postvaccination." Resp. Ex. A at 5 (quoting Pet. Ex. 63 at 9). Dr. Fujinami also cited Mailand and Frederiksen, discussed above, who reported no increased risk of MS relapse following seasonal flu or H1N1 vaccination. Resp. Ex. E at 3 (citing Resp. Ex. A, Tab 4).

Next, Dr. Fujinami discussed molecular mimicry and MS relapse. He addressed Dr. Steinman's BLAST search and homology of six shared of nine identical amino acids between gliomedin and nucleoprotein in the flu B virus. Tr. 145. Dr. Fujinami explained that the flu B virus nucleoprotein sequence (KKTSGNAFI) is "conserved among all [flu] B viruses," meaning all seasonal flu vaccines contain this sequence. Resp. Ex. E at 1; see also Tr. 145-46. Although he agreed that seasonal flu vaccines contain varying amounts of nucleoprotein each year, he opined that the amount of nucleoprotein is insufficient to induce autoimmune disease. Tr. 148, 162.

In support of this opinion, Dr. Fujinami, using Ahmed et al., calculated there would be approximately 15.6 micrograms of nucleoprotein in the flu vaccine for 2016-2017. Resp. Ex. G at 2; Tr. 150 (citing Pet. Ex. 52). He then compared this amount with the amount of APL (mimics myelin basic protein) given to patients in the Bielekova et al. and Kappos et al. studies. Resp. Ex. G at 2; Tr. 150-52; see also Resp. Ex. E, Tab 3; Pet. Ex. 57). The Bielekova et al. patients were treated with 50 mg which was decreased to 5 mg, and the Kappos et al. patients were treated with 5 mg, 20 mg, or 50 mg. Resp. Ex. G at 2; Tr. 150-52. Dr. Fujinami noted that 5 mg was 300 times the amount of nucleoprotein in the flu vaccine, and 50 mg was 3,000 times the amount of nucleoprotein in the flu vaccine. Resp. Ex. G at 2; Tr. 150-52. He also noted that in the Kappos et al. study, the patients who received 5 mg of APL (300 times the amount of

[59] Panos Stathopoulos et al., Autoimmune Antigenic Targets at the Node of Ranvier in Demyelinating Disorders, 11 Nature Revs. Neurology 143 (2015).

[60] Anne Desmazieres et al., Differential Stability of PNS and CNS Nodal Complexes When Neuronal Neurofascin Is Lost, 34 J. Neurosci. 5083 (2014).

nucleoprotein in the flu vaccine) had "no enhancing lesions and an actual decrease in MS lesions" after treatment. Tr. 152; see also Resp. Ex. G at 2.

With regard to Dr. Steinman's IEDB search, Dr. Fujinami tried but was unable to confirm Dr. Steinman's results. Resp. Ex. G at 2-4; Tr. 155-56. When he inputted the KSK sequence, no results were found. Resp. Ex. G at 2-4. Dr. Fujinami determined Dr. Steinman shifted the sequence to begin with GNAFI (GNAFIGKKNFQI), a sequence Dr. Steinman first mentioned at the hearing, "in order to find a single reference." Id. at 4; see also Tr. 156, 176-77. He added that the IEDB match Dr. Steinman found[61] does not necessarily mean the patients in that study developed a neuroinflammatory disease, only that individuals can or did respond to the peptide. Tr. 180.

Another point raised by Dr. Fujinami relates to how the purported mimic is presented to the immune system. Resp. Ex. E at 2. "In most if not all the models where molecular mimicry has been used to induce an autoimmune disease, an adjuvant such as [complete Freund's adjuvant] or an actual infection is required."[62] Id. (quoting Pet. Ex. 44 at 2). Thus, the type of adjuvant (if present) or actual infection is important for induction of neuroinflammatory autoimmune disease. Id.; Tr. 153-54; see also Resp. Ex. E, Tab 1 (where peptides of myelin basic protein were combined with incomplete Freund's adjuvant and did not lead to exacerbation of disease).[63] Dr. Fujinami also addressed the Gautam et al. studies and opined they are not relevant to Dr. Steinman's theory because "very powerful adjuvants"[64] were used to induce EAE, and "without those very powerful adjuvants, . . . autoimmune disease [is not] being produced." Tr. 153 (citing Pet. Exs. 46-48). The flu vaccine at issue here did not contain an adjuvant, nor did it contain a live virus. Tr. 154; Resp. Ex. A at 5. Therefore, Dr. Fujinami opined these studies are not analogous nor do they provide support for Dr. Steinman's theory. Tr. 155; Resp. Ex. A at 5. In summary, Dr. Fujinami testified that the lack of sufficient nucleoprotein combined with the absence of powerful adjuvants, means that the flu vaccine is not capable of generated the "robust immune response" required by Petitioner's theory. Tr. 162; Resp. Ex. A at 4.

ii. Loving Factor Five/Althen Prong Two

Dr. Fujinami opined Petitioner's flu vaccination on October 7, 2016 "did not aggravate an exacerbation of [MS]." Tr. 143; see also Resp. Ex. G at 5.

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[61] See Pet. Ex. 75.

[62] Dr. Fujinami testified that the flu infection "may" trigger an MS relapse. Tr. 166.

[63] Amitabh Gaur et al., Amelioration of Autoimmune Encephalomyelitis by Myelin Basic Protein Synthetic Peptide-Induced Anergy, 258 Science 1491 (1992).

[64] He defined an adjuvant as "a compound or substance that potentiates the immune response to the antigen that you are injecting or trying to elicit an immune response to." Tr. 152.

Dr. Fujinami asserted that because Petitioner received yearly flu vaccinations as part of his employment, and the flu B nucleoprotein sequence is in all flu B viruses, any seasonal flu vaccine Petitioner received contained the same nucleoprotein sequence and same mimicking sequence presented in the vaccine at issue in this case. Resp. Ex. E at 1-2. Thus, he questioned why, after years of receiving a flu vaccine, Petitioner did not develop MS or exacerbations of MS following each of his previous flu vaccinations. Id. at 2. According to Dr. Fujinami, if Dr. Steinman's theory was correct, each time Petitioner received a flu vaccine, he would have developed an MS exacerbation, which did not occur. Tr. 146; see also Resp. Ex. E at 2.

Additionally, Dr. Fujinami noted that unlike the studies where molecular mimicry induced disease in the context of adjuvants or infectious illness, Petitioner's flu vaccine did not contain an adjuvant or a live virus. Tr. 154.

Dr. Fujinami opined that the exacerbation of MS in Petitioner was "more like than not a coincidental event that happened by chance." Resp. Ex. A at 5. He cited to Miller et al., a flu vaccination study in patients with relapsing-remitting MS, for their determination that flu vaccination in MS patients was "neither associated with an increased exacerbation rate in the postvaccination period nor a change in disease course over the subsequent [six] months." Id. (quoting Resp. Ex. A, Tab 5 at 1).

iii. Loving Factor Six/Althen Prong Three

Dr. Fujinami stated that Petitioner received a flu vaccine on October 7, 2016, and "[a]bout [four] weeks after vaccination, [] Petitioner developed clinical signs consistent with neuroinflammatory disease," later diagnosed as MS. Resp. Ex. A at 1. He opined this timing was "more likely than not" coincidental. Id. at 5.

3. Respondent's Expert, Dr. Amanda Piquet[65]

a. Background and Qualifications

Dr. Piquet is a board-certified neurologist with subspeciality training in autoimmune neurology and neuroimmunology. Resp. Ex. C at 1. She received a B.S. in Biology at West Chester University of Pennsylvania and an M.D. from Pennsylvania State College of Medicine. Resp. Ex. D at 1. Thereafter, she completed an internal medicine internship at Massachusetts General Hospital, a neurology residency at Brigham & Woman's Hospital and Massachusetts General Hospital, and an autoimmune neurology/neuroimmunology fellowship at the University of Utah Healthcare. Id. Dr. Piquet has been a professor in the neurology department at the University of Colorado since 2017. Id. She has published on autoimmune neurology and neuroimmunology and is an author of over 30 peer-reviewed publications, with a majority focusing on autoimmune neurological disorders like MS. Id. at 6-9; Resp. Ex. C at 1. She is "regularly involved in the care of patients with various neuroimmunological conditions including [MS], transverse myelitis, neuromyelitis optic spectrum disorder [], autoimmune

[65] Dr. Piquet testified at the hearing and submitted two expert reports. Tr. 204; Resp. Exs. C, F.

encephalitides[,] as well as other antibody-mediated disease of the central and peripheral nervous system including anti-MOG antibody disease." Resp. Ex. C at 1; see also Tr. 207.

b. Opinion

Dr. Piquet agreed that Petitioner's diagnostic workup, including the lesions on MRI and presence of oligoclonal bands, was consistent with MS. Resp. Ex. C at 6; Tr. 211. However, she opined Petitioner's flu vaccine "more likely than not did not cause [Petitioner] to . . . experience[] a significant aggravation of previously stable and asymptomatic MS." Resp. Ex. C at 7.

Like Dr. Steinman, Dr. Piquet opined that it was "unlikely" that Petitioner had CIDP because his EMG did not show evidence of peripheral demyelination, and his CSF profile was consistent with MS, and not CIDP. Resp. Ex. C at 6. Further, Petitioner was seen by Dr. Bucelli, an expert in the field, and he concluded that Petitioner did not have CIDP. Id.

i. Loving Factors One, Two, and Three[66]

Dr. Piquet opined Petitioner had long-standing MS. Tr. 211-12, 219. She further opined that Petitioner did not have a relapse or significant aggravation of his MS after vaccination. Tr. 209; Resp. Ex. C at 7.

She explained that MS is an "autoimmune or neuroinflammatory condition" characterized by "relapsing-remitting" episodes presenting as "neurological deficit[s]" and "contrast-enhancing lesions on [] brain MRI." Tr. 209-10. There is "a discrete inflammatory event," followed by improvement, but then over time, "usually over the course of years, patients can accumulate disability and have disability progression." Tr. 210. In this form of progressive disease, especially later in the disease course occurring with age, "patients can have a secondary progressive phrase." Id. The "key features of MS are defined by the McDonald criteria" as "events that are separated in time and space." Id. (citing Resp. Ex. C, Tab 1 at 2). Dissemination in time is evidenced by lesions of varying ages and dissemination of space requires "lesions in distinct anatomical locations." Resp. Ex. C, Tab 1 at 2. Dr. Piquet noted the criteria can be met with "inflammation in the spinal fluid, like oligoclonal bands," or MRI findings. Tr. 213-14.

The 2017 McDonald criteria regarding exacerbations/relapses requires "objective findings . . . reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 h[ours], with or without recovery, and in the absence of fever or infection." Resp. Ex. C, Tab 1 at 2. Clinically, a patient with a relapse due to a focal event will have symptoms dependent on the site of the lesion. Tr. 214. Examples include weakness on one side, dizziness, or vision loss. Id. A contrast MRI will show

[66] Dr. Piquet focused on the issue of relapse/significant aggravation, and did not offer opinions refuting the causal mechanisms alleged by Petitioner about whether the flu vaccine can cause, or in this case, did cause MS. Those issues were addressed by Dr. Fujinami.

enhancement consistent with the inflammation and new focal lesion. Id. There may be a "combination of symptoms" due to multiple lesions in different areas. Tr. 215.

According to Dr. Piquet, the current thinking is that MS is a two-stage disease with inflammation followed by progression and a "neurodegenerative picture." Tr. 212; see also, e.g., Resp. Ex. F, Tab 3 at 1 ("[R]ecent results of clinical trials in secondary progressive MS suggest that there may be different pathogenic mechanisms in MS: an inflammatory mechanism for relapses and a more degenerative mechanism for progressive disease."); Resp. Ex. F, Tab 7;[67] Resp. Ex. F, Tab 8.[68] The biomarkers or evidence of inflammation seen on brain or spinal cord MRIs show active inflammation, indicating that the immune system is breaking down myelin and attacking nerves, resulting in a breach of the blood-brain barrier that results in enhancement which "light[s] up" or appears "bright" on MRI scans. Tr. 212, 215. A contrast-enhancing lesion suggests "an acute demyelinating event." Tr. 215.

Dr. Piquet explained that over time, the inflammation affects not only the myelin sheath but also the axon and results in destruction of neurons, with symptoms that "slowly progress[es] over the course of months to years." Tr. 213. Progressive disease or neurodegeneration may be characterized by cognitive impairment and fatigue. Id. For support, she cited Schwartz et al., who found that "[l]oss of cognitive reserve may explain the onset of progressive disease in MS." Resp. Ex. C, Tab 13 at 1.[69]

Turning to Petitioner's course, Dr. Piquet opined that his MS was "smoldering for 30+ years given his neurological event at the age of 30 years old and the known natural history of MS." Tr. 211-12, 219; Resp. Ex. C at 7. She agreed that the neurological events Petitioner described around 1984 (at 30 years old) and in 2000 were compatible with MS although confirmatory diagnostic testing was not conducted. Tr. 237-39, 243.

Dr. Piquet summarized Petitioner's clinical course post-vaccination. See Resp. Ex. C at 2-6. Petitioner received the flu vaccination on October 7, 2016. Id. at 5. He noted bilateral tingling and numbness in his feet four weeks later. Id. at 2, 5. Petitioner did not seek neurological care for his initial symptoms of numbness and tingling and he did not seek neurological care for eight months. Resp. Ex. F at 4. Petitioner first presented to a treating physician in June 2017, when he saw Dr. Elmore. Resp. Ex. C at 2, 5.

Petitioner's initial brain and spinal cord MRIs were done September 13, 2017. Dr. Piquet testified they showed MS due to the "characteristic lesions" located in the brain and spinal cord.

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[67] Emmanuelle Leray et al., Evidence for a Two-Stage Disability Progression in Multiple Sclerosis, 133 Brain 1900 (2010).

[68] Jeroen Van Schependo et al., Detecting Neurodegenerative Pathology in Multiple Sclerosis Before Irreversible Brain Tissue Loss Sets In, 8 Translational Neurodegeneration 1 (2019).

[69] Carolyn E. Schwartz et al., Cognitive Reserve ad Symptom Experience in Multiple Sclerosis: A Buffer to Disability Progression Over Time?, 94 Archives Physical Med. & Rehab. 1971 (2013).

Tr. 219. They also showed T1 black holes, suggestive of "very old lesions, [and] chronic MS." Id. Black holes indicate "destruction of the neurons." Id. Dr. Piquet testified these findings were consistent with long-standing MS. Tr. 219-20, 238. Further, the study showed "characteristic lesions" of MS, "separated in different areas of the brain." Tr. 242. Petitioner also had "patchy [spinal] cord signal abnormalities" scattered throughout the spinal cord, indicating old demyelinating lesions. Tr. 242-43. Petitioner did not have "active enhancing lesions that would indicate active demyelination" to support a diagnosis of a relapse or exacerbation of preexisting MS. Tr. 219-20.

Dr. Piquet did not dispute the fact that Petitioner developed neurologic symptoms after his flu vaccine. Tr. 244. She explained that Petitioner "had bilateral involvement that ascended slowly, from his feet to his knees, of sensory changes." Tr. 226. Dr. Piquet noted, however, that because these changes occurred over a period of several weeks to months, they are not typical for a demyelinating attack in MS. Tr. 226-27. She explained that usually in MS, when there is a new demyelinating lesion, there is a subacute onset, with symptoms "starting and ramping up over the course of 24 hours[] [to] a couple of days." Tr. 226. Without an MRI taken at the time, Dr. Piquet was unable to attribute Petitioner's symptoms to MS. Tr. 227. Due to Petitioner's presentation, she opined the most common cause of his symptoms would be neuropathy. Id. However, based on his EMG, Petitioner did not have CIDP. Id.

In summary, Dr. Piquet opined that "the progression of how [Petitioner's] symptoms presented [was] not suggestive of an acute relapse." Tr. 227. She explained that Petitioner had relapsing-remitting MS because he recovered after each neurologic event prior to 2016. Tr. 247. Then Petitioner transitioned to the progressive phase of MS, known as secondary progressive MS. Id.; see also Resp. Ex. F at 4. Additionally, she opined that cognitive changes are "thought to be [due to an] accumulation of lesions leading to disability" that are seen later in the disease course with aging. Tr. 221-22. According to Dr. Piquet, cognitive changes can be considered a relapse/exacerbation of MS in young patients in the form of encephalopathy, but that differs from a "slow progressive cognitive decline" as seen here. Tr. 222.

As to Loving factor three, Dr. Piquet opined Petitioner did not experience a significant aggravation or exacerbation of MS following his October 2016 flu vaccination because there was no objective evidence to support such finding. Resp. Ex. C at 6-7; Resp. Ex. F at 2, 4; Tr. 209, 213.

She explained Petitioner's MRIs did not show evidence of active disease. Resp. Ex. C at 6-7; Resp. Ex. F at 4; Tr. 218-19. Petitioner's initial MRIs in September 2017, ten months after Petitioner's alleged onset of symptoms, did not show evidence of enhancing lesions to indicate active demyelination. Resp. Ex. F at 4; Tr. 219. Instead, the MRIs demonstrated "many chronic features," including "confluent T2/FLAIR changes and T1 black holes." Resp. Ex. C at 7. She explained that T1 black holes, or T1 hypointensity, "are suggestive of very old lesions" and characteristic of chronic MS. Tr. 219, 241. Because there was no evidence of active demyelination on MRI, she opined Petitioner did not experience an exacerbation or significant aggravation. Tr. 219-20.

Dr. Piquet opined that Petitioner's "progressive symptoms of fatigue, numbness, and cognitive changes reported in the months after vaccination could all be attributed to expected evolution and progression of long-standing MS." Resp. Ex. C at 7. She acknowledged MS can still progress or worsen without active demyelination, but would not be a "significant aggravation" without evidence of active disease on MRI. Tr. 219-25. Further, she opined a slow progression of symptoms over months, as seen in Petitioner, did not fit with an acute relapse. Tr. 245.

Additionally, Dr. Piquet noted that for "significant aggravation," she would have expected evidence of ongoing, active inflammation (i.e., MRI evidence of such) when Petitioner was reporting "ongoing, worsening neurological symptoms (i.e., later [] reports of cognitive complaints)." Resp. Ex. F at 4. On cross-examination, Dr. Piquet acknowledged that active demyelination would only be seen on MRI for up to three months, and that Petitioner received his first MRIs in September 2017, ten months after his alleged onset. Tr. 232. However, she maintained that there should be MRI findings to explain the "slowly progressive symptoms over the course of months." Id.

Moreover, she opined Petitioner's MRIs were "not [] compatible with a defined MS relapse" using the 2017 McDonald criteria due to the lack of evidence of active demyelination on MRI. Resp. Ex. F at 2 (citing Resp. Ex. C, Tab 1 at 2). A relapse/exacerbation of MS under the McDonald criteria require "objective findings . . . reflecting a focal or multifocal inflammatory demyelinating event." Resp. Ex. C, Tab 1 at 2. Objective evidence is defined as "[a]n abnormality on neurological examination, imaging (MRI or optical coherence tomography), or neurophysiological testing (visual evoked potentials) that corresponds to the anatomical location suggested by the symptoms." Id.

Lastly, she opined the findings on EMG/NCS do not pertain to MS, and in fact, would be evidence of an alternative reason for Petitioner's numbness and tingling. Resp. Ex. F at 2. In June 2017, a work-up revealed evidence of a sensorimotor axonal neuropathy, which Dr. Piquet opined "is not a neurological presentation compatible with a MS relapse" because it is not "a focal or multifocal inflammatory demyelinating event" required by the McDonald criteria. Id. at 4-5 (quoting Resp. Ex. C, Tab 1 at 2); see also Tr. 233. She also noted that an axonal neuropathy relates to the PNS, whereas MS is a disease of the CNS. Tr. 233. She maintained the neuropathy and MS are unrelated, with differing etiologies. Tr. 234. Dr. Piquet agreed that one could have both neuropathy and MS, but in that event, the conditions would have different "underlying pathophysiology" and different causes. Id.

ii. Loving Factor Six/Althen Prong Three

Dr. Piquet agreed the records and Petitioner's statements place onset of numbness and tingling in late 2016. Tr. 34; Resp. Ex. C at 2. She opined that "more likely than not" the temporal association between the onset of these symptoms and vaccination was "coincidental." Resp. Ex. C at 8.

Moreover, as described above, the symptoms that Petitioner complained of post-vaccination occurred over a period of several weeks to months, which is not characteristic for a

relapse in MS. Tr. 226-27. MS relapse usually has a subacute onset, with symptoms occurring over the course of a day to a couple of days. Tr. 227. Without an MRI taken at the time, Dr. Piquet was unable to attribute Petitioner's symptoms that occurred post-vaccination to MS. Id.

III. DISCUSSION

A. Standard of Adjudication—Factual Issues

A petitioner must prove, by a preponderance of the evidence, the factual circumstances surrounding his claim. § 13(a)(1)(A). To resolve factual issues, the special master must weigh the evidence presented, which may include contemporaneous medical records and testimony. See Burns v. Sec'y of Health & Hum. Servs., 3 F.3d 415, 417 (Fed. Cir. 1993) (explaining that a special master must decide what weight to give evidence including oral testimony and contemporaneous medical records). Contemporaneous medical records, "in general, warrant consideration as trustworthy evidence." Cucuras v. Sec'y of Health & Hum. Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). But see Kirby v. Sec'y of Health & Hum. Servs., 997 F.3d 1378, 1382 (Fed. Cir. 2021) (rejecting the presumption that "medical records are accurate and complete as to all the patient's physical conditions"); Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 538 (2011) ("[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance." (quoting Murphy v. Sec'y of Health & Hum. Servs., 23 Cl. Ct. 726, 733 (1991), aff'd per curiam, 968 F.2d 1226 (Fed. Cir. 1992))), recons. den'd after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 503 F. App'x 952 (Fed. Cir. 2013).

There are situations in which compelling testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. Campbell v. Sec'y of Health & Hum. Servs., 69 Fed. Cl. 775, 779 (2006) ("[L]ike any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking."); Lowrie v. Sec'y of Health & Hum. Servs., No. 03-1585V, 2005 WL 6117475, at *19 (Fed. Cl. Spec. Mstr. Dec. 12, 2005) ("[W]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent." (quoting Murphy, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

Despite the weight afforded to medical records, special masters are not bound rigidly by those records in determining onset of a petitioner's symptoms. Valenzuela v. Sec'y of Health & Hum. Servs., No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); see also Eng v. Sec'y of Health & Hum. Servs., No. 90-1754V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb. 18, 1994) ("[Section 13(b)(2)] must be construed so as to give effect also to § 13(b)(1) which directs the special master or court to consider the medical records (reports, diagnosis, conclusions, medical judgment, test reports, etc.), but does not require the special master or court to be bound by them." (emphasis omitted)).

B. Standards for Adjudication—Causation

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Hum. Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

In particular, Petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley, 991 F.2d at 1575.

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63, aff'd, 586 F. App'x 588 (Fed. Cir. 2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

To receive compensation through the Program, Petitioner must prove either (1) that he suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that he suffered an injury that was actually caused by or significantly aggravated by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Because Petitioner does not allege he suffered a Table Injury, he must prove his flu vaccine significantly aggravated his injury. See Loving, 86 Fed. Cl. at 142-44.

The causation theory must relate to the injury alleged. Petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether Petitioner is entitled to compensation, the special master shall consider all materials in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioner's favor when the evidence weighs in his favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen v. Sec'y of Health & Hum. Servs., 418 F.3d 1274, 1280 (Fed. Cir. 2005) (noting that "close calls" are resolved in Petitioner's favor).

Testimony that merely expresses the possibility—not the probability—is insufficient, by itself, to substantiate a claim that such an injury occurred. See Waterman v. Sec'y of Health & Hum. Servs., 123 Fed. Cl. 564, 573-74 (2015) (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard). The Federal Circuit has made clear that the mere possibility of a link between a vaccination and a petitioner's injury is not sufficient to satisfy the preponderance standard. Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

C. Standards for Adjudication—Significant Aggravation

The elements of an off-Table significant aggravation case are set forth in Loving. See Loving, 86 Fed. Cl. at 142-44; see also W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (holding that "the Loving case provides the correct framework for evaluating off-table significant aggravation claims"). The Loving court combined the Althen test, which defines off-Table causation cases, with a test from Whitecotton. Whitecotton v. Sec'y of Health & Hum. Servs., 17 F.3d 374 (Fed. Cir. 1994), rev'd sub nom., Shalala v. Whitecotton, 514 U.S. 268 (1995) (concerning on-Table significant aggravation cases). The resultant test has six components, which are:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144.

The statute defines "significant aggravation" as "any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 33(4).

IV. SIGNIFICANT AGGRAVATION ANALYSIS

A. Loving Factor One: What Was Petitioner's Condition Prior to Administration of the Vaccine?

The first step in the Loving test is to determine Petitioner's condition prior to the administration of his flu vaccine on October 7, 2016.

The parties stipulated that prior to Petitioner's flu vaccination on October 7, 2016, Petitioner "was not experiencing any symptoms related to [MS]." Joint Prehearing Submission at 1. The undersigned agrees with the parties that Petitioner was not experiencing any MS-related symptoms prior to vaccination and was in good health.

Although Petitioner was not experiencing MS symptoms at the time of his flu vaccination, the experts and treating physicians agreed that Petitioner's neurological event in 1984, when he was 30, characterized by ataxia, slurred speech, and gross motor dysfunction was more likely than not the initial presentation of his MS. Petitioner's symptoms of MS were preceded by an EBV infection thought to be mono encephalitis. The symptoms took approximately one year to resolve, and after that, Petitioner recovered and was neurologically intact.

In 2000, Petitioner had neurological symptoms while he was building a retaining wall. He lost his ankle reflex, had mild foot drop, and developed numbness and tingling in his right leg. These symptoms resolved after a couple of weeks. The experts did not reach a consensus opinion about whether this episode represented a relapse of MS. Since the undersigned's Decision does not turn on this episode, no finding is reached regarding whether it was a relapse of Petitioner's MS.

The undersigned finds that prior to his flu vaccination on October 7, 2016, Petitioner had long-standing MS, with an initial onset in 1984 at age 30. At the time of his vaccination, he was not experiencing symptoms consistent with MS.

B. Loving Factor Two: What Is Petitioner's Current Condition (or His Condition Following the Vaccination, If Also Pertinent)?

The second part of the Loving test is to determine the Petitioner's condition following the flu vaccination. Loving, 86 Fed. Cl. at 144.

Petitioner testified that approximately three to four weeks after receiving his flu vaccination on October 7, 2016, he began to experience "extremely subtle numbness and tingling" in his feet. Tr. 11-12. Initially, his symptoms were "very subtle" that he wondered "if they were real or not." Pet. Ex. 26 at ¶ 8. Petitioner did not seek medical treatment for these symptoms. There is no evidence that these subtle symptoms affected his ability to work or his activities of daily living.

Around December 2016 to January 2017, Petitioner's numbness and tingling became more pronounced and gradually ascended his legs. He also developed fatigue, mental fogginess, and some mild memory issues. Over the next several months, his symptoms worsened. He saw Dr. Elmore, a neurologist, on June 14, 2017 (eight months after his flu vaccination). Physical examination revealed that Petitioner had normal muscle strength, muscle tone, gait, and balance. His sensory examination was abnormal with slightly decreased sensation to light touch in a distal patterns in his feet. He also had slightly decreased reflexes with nearly absent reflexes in his ankles.

Subsequent workup was performed from June to September 2017. CSF revealed oligoclonal bands. MRIs performed on September 13, 2017 were suggestive of MS but did not show enhancing lesions. At a follow up visit to Dr. Elmore on October 4, 2017, Petitioner complained of worsening numbness, weakness, cognitive issues, fatigue, and gait problems.

The undersigned finds that four to six weeks after vaccination, Petitioner had very subtle numbness and tingling in his feet. These symptoms were so subtle that Petitioner stated he questioned whether they were real. There is no evidence that these subtle symptoms affected his ability to work full time or conduct his normal activities or activities of daily living. These symptoms did not progress until December 2016 or January 2017. However, there is no evidence that the increased numbness that Petitioner experienced in December 2016 was significant enough to affect his ability to work full time or conduct his activities of daily living.

Petitioner's wife, Mrs. Juranek, averred that in February and March 2017, Petitioner began napping, which was unusual for him. This evidence supports Petitioner's recollection of fatigue, and that it began approximately February and March 2017. Mrs. Juranek stated that Petitioner's numbness and tingling worsened in April and May 2017, consistent with Petitioner's testimony that he obtained blood work in May 2017 due to his concerns that his symptoms were worsening.

C. Loving Factor Three: Does Petitioner's Current Condition (or Condition After Vaccination) Constitute a "Significant Aggravation" of His Condition Prior to Vaccination?

The next factor of the Loving test is to determine whether there is a "significant aggravation" of Petitioner's condition by comparing his condition before vaccination to his condition after vaccination. The statute defines "significant aggravation" as "any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 33(4).

Using this definition, the undersigned finds that, based on the facts and circumstances here, Petitioner did not have a significant aggravation of his underlying condition until the summer or fall of 2017. On September 6, 2017, Petitioner reported worsening numbness and tingling that was ascending and flank pain but his examination was normal, as was his coordination, strength, muscle tone, and gait. However, on October 4, 2017, Petitioner reported worsening numbness, weakness in his arms, cognitive problems, and difficulty walking later in the day. When Petitioner saw Dr. Chahin on November 9, 2017, he reported that by summer 2017, he had numbness in his hands, weakness in his arms, and significant fatigue. When Petitioner saw Dr. Elmore on December 6, 2017, he opined that Petitioner was permanently disabled given his MRI findings and his symptoms.

The undersigned finds that in the first two months after his flu vaccination, Petitioner's condition did not constitute a significant aggravation as it was not characterized by "markedly greater disability, pain, or illness accompanied by [a] substantial deterioration in [his] health." § 33(4). There is no indication that Petitioner, his colleagues, or his wife observed that he was suffering from a disability or illness that caused a substantial deterioration in his health as compared to before his vaccination. At the earliest, it was not until February 2017, when his wife noted that Petitioner was napping during the day time, that there is evidence of a change in his behavior reflective of his progressive condition, which impacted his daily life.

D. Loving Factor Four/Althen Prong One: Medical Theory of Causation

The fourth Loving factor has its origins in Althen prong one, and Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1379; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon, 941 F.3d at 1359; see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support his theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339 at 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994)

(stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds Petitioner failed to provide preponderant evidence of a sound and reliable theory to explain how the flu vaccine can significantly aggravate MS. There are several reasons for this finding.

First, Petitioner's proposed mechanism of molecular mimicry based on homology between the flu vaccine component (nucleoprotein of B/Brisbane/60/2008-like virus) and gliomedin falls short and has not been proven by preponderant evidence because the medical literature and evidence filed herein does not preponderantly establish that gliomedin is present in the CNS, or if it is, that it plays a role in disease pathogenesis so as to significantly aggravate MS. Further, as to these issues, Respondent's expert Dr. Fujinami was more persuasive.

Petitioner's causal theory relies on gliomedin to be present in the CNS, where it is the binding partner of NF186. The Eshed et al. paper is the evidence cited by Petitioner for the proposition that gliomedin is present in the CNS. In the paper, the authors make a distinction between the PNS and the CNS, and they conclude that their findings related to gliomedin are limited to the PNS. To quote the authors, "[t]aken together, our findings suggest that gliomedin acts as a local glial cue, which triggers the assembly of the nodes of Ranvier in the PNS." Pet. Ex. 36 at 11. Further, Eshed et al. states that "[d]ifferent mechanisms may operate in the CNS, where nodal clustering requires the presence of oligodendrocytes." Id. at 13. Thus, the research by Eshed et al. does not establish that gliomedin is present in the CNS, but if it is, the authors clearly state that different mechanisms operate in the CNS, and that oligodendrocytes are the relevant players, not gliomedin.

After the hearing, Dr. Steinman provided an excerpt from the Human Protein Atlas, showing that low amounts of gliomedin protein was expressed in the cerebral cortex, caudate, colon, and high amounts were expressed in soft tissue. Gliomedin RNA was expressed in the cerebral cortex, with smaller amounts expressed in connective and soft tissue and elsewhere. This evidence established that there are low amounts of gliomedin expressed in the cerebral cortex and caudate of the brain, and no evidence of gliomedin in the spinal cord. It also shows gliomedin RNA is expressed in the cerebral cortex. But again, gliomedin is not found in the spinal cord. Thus, it is not clear how Dr. Steinman's mechanistic theory founded on homology between a vaccine component and gliomedin can cause MS, if gliomedin is present in low amounts in two areas of the brain (cortex and caudate) and not found in the spinal cord.

On the question of whether gliomedin is present in the brain and spinal cord, Dr. Fujinami was more persuasive. He opined that gliomedin is not present in the CNS, and that there is a counterpart to gliomedin in the CNS. He filed two papers that identified the proteins which have been found in the CNS, consistent with his opinions at hearing. Desmazieres et al. compared what happens when neurofascin is lost at nodal complexes in the PNS and CNS. Resp. Ex. H at 1. Relative to this case, the authors described brevican is in the CNS and gliomedin is in the PNS. Id. at 1, 3, 4 fig.4, 5. Similarly, Stathopoulos et al. stated that "[i]n the PNS, [] two proteins [NF186 and neuronal cell adhesion molecule Nr-CAM] interact with each other and with the matrix protein gliomedin to promote microvilli-axon attachment," which

"stabilizes the nodal structure." Resp. Ex. I at 2. "In the CNS, several extracellular matrix proteins, including [] oligodendrocytic proteins . . . and brevican, and the neuronal brain link protein 1 (Bral1) and neurocan, might have similar roles to gliomedin." Id. at 2, 4 tbl.1. Overall, the evidence fails to establish that gliomedin plays a role in the CNS as suggested by Dr. Steinman.

In addition to his reliance on gliomedin, Dr. Steinman also opined that there was "too much" nucleoprotein in the vaccine and that this excessive amount played a causal role. However, Dr. Steinman did not provide any foundational evidence to establish what amount of nucleoprotein constitutes an excessive amount or that the vaccine at issue here contained an excessive amount of nucleoprotein. Thus, this aspect of his opinion was speculative and conclusory.

When evaluating whether petitioners have carried their burden of proof, special masters consistently reject "conclusory expert statements that are not themselves backed up with reliable scientific support." Kreizenbeck v. Sec'y of Health & Hum. Servs., No. 08-209V, 2018 WL 3679843, at *31 (Fed. Cl. Spec. Mstr. June 22, 2018), mot. for rev. denied, 141 Fed. Cl. 138, aff'd, 945 F.3d 1362 (Fed. Cir. 2020). The undersigned will not rely on "opinion evidence that is connected to existing data only by the ipse dixit of the expert." Prokopeas v. Sec'y of Health & Hum. Servs., No. 04-1717V, 2019 WL 2509626, at *19 (Fed. Cl. Spec. Mstr. May 24, 2019) (quoting Moberly, 592 F.3d at 1315).

Moreover, Respondent filed studies that examined whether the flu vaccine increases the risk of MS relapse, and these studies also do not show a causal association. For example, Miller et al. found "[flu] immunization in MS patients is neither associated with an increased exacerbation rate in the postvaccination period nor a change in disease course over the subsequent [six] months." Resp. Ex. A, Tab 5 at 1. Mailand and Frederiksen found one study that reported an increase in relapse three weeks after vaccination; however, the authors determined this study "lack[ed] statistical power, since it [was] based on only 18 patients." Resp. Ex. A, Tab 4 at 2, 13. The authors concluded there is "no association" between the flu vaccine or H1N1 vaccine and MS relapse. Id. at 2.

And, at the hearing, Dr. Steinman testified that there is "no epidemiologic evidence" showing that there is an increased risk of MS relapse after receipt of the flu vaccination. Tr. 131.

Although a petitioner need not make a specific type of evidential showing (i.e., epidemiologic studies) to satisfy his burden, special masters shall still consider and weigh the evidence in the record, including the epidemiological studies filed. See § 13(b)(1) (indicating the special master shall consider all materials in the record); Capizzano, 440 F.3d at 1325-26; Grant v. Sec'y of Health & Hum. Servs., 956 F.2d 1144, 1149 (Fed. Cir. 1992) (finding "epidemiological studies are probative medical evidence relevant to causation" and "considerable weight [is] due to epidemiological studies in the absence of direct evidence of actual causation"); see also Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence.").

Finally, there are other Program cases with reasoned analyses regarding whether the flu vaccination can aggravate MS via molecular mimicry, where the special masters denied entitlement. One of these cases was appealed to the Federal Circuit, who affirmed the judgment of the Court of Federal Claims upholding the special master's decision denying compensation. See W.C., 704 F.3d 1352. In W.C., the petitioner alleged that a flu vaccine caused or significantly aggravated MS via the mechanism of molecular mimicry.[70] Id. at 1354-55. The Federal Circuit found that the special master "correctly required additional evidence showing that molecular mimicry can cause the [flu] vaccine to significantly aggravate [MS]." Id. at 1360. Moreover, Petitioner "did not provide evidence that any peptide from the [flu] vaccine he received was cross-reactive with myelin basic protein-specific T cells" thought to trigger the cross-reactive immune response. Id. Thus, the Federal Circuit held that the special master's finding as to the lack of evidence of a supportive medical theory was not arbitrary or capricious. Id. at 1361.

Since W.C. in 2013, there have been no other Federal Circuit opinions addressing the mechanism of molecular mimicry in the context of a flu vaccine and MS. There have been cases decided by special masters on the issue of whether a flu vaccination can significantly aggravate MS where molecular mimicry was posited as the causal theory; however, these cases involved different facts and evidence.[71] Further, rulings and decisions by other special masters are not binding on the undersigned. See Boatmon, 941 F.3d at 1358; Hanlon v. Sec'y of Health & Hum. Servs., 40 Fed. Cl. 625, 630 (1998), aff'd, 191 F.3d 1344 (Fed. Cir. 1999).

In summary, Petitioner has failed to offer a sound and reliable medical theory in support of his claim. Thus, the undersigned finds Petitioner has failed to provide preponderant evidence with respect to the Loving Factor four and Althen Prong one.

E. Loving Factor Five/Althen Prong Two: Logical Sequence of Cause and Effect

Under Loving factor five and Althen prong two, Petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as

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[70] In W.C., the special master also found that the onset of Petitioner's MS preceded vaccination, and thus could not have caused it. W.C., 704 F.3d at 1356.

[71] See, e.g., Robinson v. Sec'y of Health & Hum. Servs., No. 14-952V, 2021 WL 2371721 (Fed. Cl. Spec. Mstr. Apr. 12, 2021); P.M. v. Sec'y of Health & Hum. Servs., No. 16-949V, 2019 WL 5608859 (Fed. Cl. Spec. Mstr. Oct. 31, 2019); Quackenbush-Baker v. Sec'y of Health & Hum. Servs., No. 14-1000V, 2018 WL 1704523 (Fed. Cl. Spec. Mstr. Mar. 14, 2018).

treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. Cucuras, 993 F.2d at 1528. Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

Regarding the fifth Loving factor/second Althen prong, the undersigned finds that Petitioner has failed to show by preponderant evidence that the flu vaccination significantly aggravated his MS.

First, Petitioner's clinical course was not consistent with a significant aggravation, as explained above. As explained by Dr. Piquet, after vaccination, Petitioner developed bilateral numbness and tingling that ascended slowly from his feet upward. These changes occurred over a period of several weeks to months, which Dr. Piquet noted is not typical for a demyelinating attack. If Petitioner had experienced a post-vaccine demyelinating event, his symptoms would have "ramp[ed] up over the course of 24 hours[] [to] a couple of days." Tr. 226.

Moreover, Petitioner did not have a clinical course that warranted medical attention for eight months. His post-vaccination symptoms were subtle, and he questioned whether they were real. He did not have any diagnostic studies performed. Although Dr. Steinman suggested that if Petitioner had undergone MRI of the brain and spinal cord after vaccination the studies may have shown enhancement consistent with demyelinating lesions, this opinion is speculative. As explained by Dr. Piquet, and recognized by the 2017 McDonald criteria, a relapse of MS is characterized by "objective findings . . . reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 h[ours]." Resp. Ex. C, Tab 1 at 2. Here there are no objective findings to show that more likely than not Petitioner had any relapse in the four to six week period post-vaccination. Petitioner did not have a typical presentation, but instead had subtle symptoms, and he had no objective findings on diagnostic testing consistent with a MS relapse. Therefore, the undersigned finds that Petitioner's clinical course does not provide preponderant evidence of a logical sequence of cause and effect.

Further, the undersigned agrees with Respondent's expert Dr. Piquet that Petitioner's worsening reflects a progression of his MS. She explained that Petitioner developed secondary progressive MS, characterized by his slow progressive cognitive decline. Her opinion is supported by Petitioner's visit to Dr. Elmore on October 4, 2017. At this visit, Petitioner complained of worsening numbness and some weakness in his arms. He also had cognitive complaints of forgetfulness and difficulty concentrating, as well as fatigue and difficulty ambulating later in the day. Pet. Ex. 1 at 26. This appears to be the first mention in the medical records of cognitive concerns.

Dr. Piquet opined that Petitioner's initial brain MRI done September 13, 2017 showed T1 black holes, suggestive of "very old lesions, [and] chronic MS." Tr. 219. He also had patchy spinal cord lesions, also indicating old demyelinating lesions. She explained that in secondary progressive MS, cognitive changes are thought to be caused by an accumulation of lesions, which are seen later in the disease course, consistent with a "slow progressive cognitive decline" as was present here. Tr. 222. She cited Schwartz et al., who reported that that loss of cognitive reserve may signal the onset of such progressive disease. Resp. Ex. C, Tab 13 at 1.

Notably, Petitioner's fatigue as reflected by his napping, was observed beginning in February 2017 by Mrs. Juranek, about four months post-vaccination. He did not report cognitive symptoms until October 2017, approximately one year after vaccination. This clinical course is consistent with Dr. Piquet's opinion that Petitioner has secondary progressive MS, and not an acute decline reflective of a relapse due to an acute demyelinating event.

Regarding Petitioner's treating physicians, two expressed opinions about causation, Dr. Elmore and Dr. Chahin. In December 2017, Dr. Elmore wrote that the flu vaccination "certainly did not cause his MS as I believe his MS was preexisting . . . . It is possible that the flu shot precipitated a flare-up which many neuroimmunologist[s] believe is possible." Pet. Ex. 4 at 19. Then, in February 2018, Dr. Elmore stated that the vaccination "could have caused a relapse of his MS." Pet. Ex. 4 at 14. At a follow-visit on July 5, 2018, Dr. Elmore wrote that the vaccination "probably" caused Petitioner's MS flare. Id. at 4. Dr. Elmore did not explain why his opinion changed from "possible" to "probable" over time.

Generally, treating physician statements are typically "favored" as treating physicians "are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" Capizzano, 440 F.3d at 1326 (quoting Althen, 418 F.3d at 1280). However, no treating physician's views bind the special master, per se; rather, their views are carefully considered and evaluated. § 13(b)(1); Snyder, 88 Fed. Cl. at 746 n.67. "As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." Welch v. Sec'y of Health & Hum. Servs., No. 18-494V, 2019 WL 3494360, at *8 (Fed. Cl. Spec. Mstr. July 2, 2019).

Here, Dr. Elmore's statements are internally inconsistent, and therefore, the undersigned finds it reasonable to give greater weight to the most contemporaneous-in-time medical records. See Cucuras, 993 F.2d at 1528 (noting that "the Supreme Court counsels that oral testimony in conflict with contemporaneous documentary evidence deserves little weight"); Doe/70 v. Sec'y of Health & Hum. Servs., 95 Fed. Cl. 598, 608 (2010); Stevens v. Sec'y of Health & Hum. Servs., No. 90-221V, 1990 WL 608693, at *3 (Cl. Ct. Spec. Mstr. Dec. 21, 1990) (noting that "clear, cogent, and consistent testimony can overcome such missing or contradictory medical records"); Vergara ex rel. J.A.V. v. Sec'y of Health & Hum. Servs., No. 08-882V, 2014 WL 2795491, at *4 (Fed. Cl. Spec. Mstr. May 15, 2014) ("Special Masters frequently accord more weight to contemporaneously-recorded medical symptoms than those recorded in later medical histories, affidavits, or trial testimony."); Campbell, 69 Fed. Cl. at 779 ("It is, of course, true that where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight.").

Opinions expressed as possibilities are not sufficient to establish causation. See, e.g., Waterman, 123 Fed. Cl. at 573-74; Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence). Moreover, an opinion by a treating physician that is not supported by a factual basis or other evidence is conclusory in nature. See Robertson v. Sec'y of Health & Hum. Servs., No. 18-554V, 2022 WL 17484980, at *17 (Fed. Cl. Spec. Mstr. Dec. 7, 2022); Cedillo v. Sec'y of Health & Hum. Servs., 617 F.3d 1328, 1347 (Fed. Cir. 2010). And special masters consistently reject conclusory expert statements. Kreizenbeck, 2018 WL 3679843, at *31.

Dr. Chahin considered and rejected the idea that the flu vaccination caused Petitioner's MS, explaining "vaccinations could trigger a relapse but do not actually cause the illness itself." Pet. Ex. 2 at 3. Dr. Chahin, however, did not opine or suggest that Petitioner had a vaccine-related relapse.

Accordingly, the undersigned finds that Petitioner's treating physicians did not provide persuasive evidence of vaccine causation.

For these reasons, the undersigned finds that Petitioner has failed to provide preponderant evidence of a logical sequence of cause and effect to satisfy his burden under Loving factor five/Althen prong two.

F. Loving Factor Six/Althen Prong Three: Proximate Temporal Relationship

The last element in the six-part Loving test has origins in Althen prong three. As stated in Loving, this element is "a showing of a proximate temporal relationship between vaccination and the significant aggravation." 86 Fed. Cl. at 144. Althen prong three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. A proximate temporal relationship has been equated to mean a "medically acceptable temporal relationship." Id. Petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disease's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen prong one). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542.

Based on the case law cited above, this factor/prong consists of two parts. Petitioner must first establish the time frame within which it is medically acceptable to infer causation. And secondly, he must show that the onset of the worsening or aggravation of his illness occurred during this time frame.

Dr. Steinman testified that four to six weeks was an appropriate timeframe for the onset of demyelinating illnesses in the PNS, citing Schonberger et al. Giving Petitioner the benefit of the doubt, the undersigned presumes that timeframe is also appropriate for a relapse of MS, a

CNS demyelinating illness. However, as explained above, the undersigned found that Petitioner did not experience a significant aggravation of his MS in the four to six weeks after vaccination. Petitioner had very subtle numbness and tingling in his feet. But these symptoms did not constitute a significant aggravation of his MS. In February and March 2017, Petitioner began napping, evidence of worsening symptoms of fatigue. Petitioner's numbness and tingling worsened in April and May 2017, and he reported cognitive complaints in October 2017. Thus, in the summer and fall of 2017, Petitioner had worsening of his symptoms, and he ultimately retired in late 2017.

Because the undersigned finds that Petitioner did not have a significant aggravation or relapse of his MS symptoms in the four to six weeks after vaccination, but instead developed a progressive worsening over months, as described by Dr. Piquet, the undersigned finds that Petitioner has failed to provide preponderant evidence satisfying Loving factor six/Althen prong three. He has failed to show that he suffered a significant aggravation of his MS within the temporal period appropriate given the proffered theory of molecular mimicry.

V. CONCLUSION

The undersigned extends her sympathy to Petitioner for the pain and suffering and disability that he has experienced due to his illness. The undersigned's Decision, however, cannot be decided based upon sympathy, but rather on the evidence and law.

For the reasons discussed above, the undersigned finds that Petitioner has failed to establish by preponderant evidence that his flu vaccination significantly aggravated his MS. Therefore, Petitioner is not entitled to compensation and the petition must be dismissed.

In the absence of a timely filed motion for review pursuant to Vaccine Rule 23, the Clerk of Court **SHALL ENTER JUDGMENT** in accordance with this Decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master